Exhibit 16

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	) MDL NO: 16-2738 (FLW)(LHG)
THIS DOCUMENT RELATES TO ALL CASES	)

****

ORAL VIDEOTAPED/REALTIMED DEPOSITION OF

ELLEN BLAIR SMITH, M.D.

JANUARY 9, 2019

VOLUME 1 OF 1

****

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ORAL AND VIDEOTAPED/REALTIMED DEPOSITION OF ELLEN BLAIR SMITH, M D , produced as a witness at the instance of the Defendants Johnson & Johnson entities, and duly sworn, was taken in the above-styled and numbered cause on January 9, 2019, from 9:24 a m to 9:23 p m , before Karen L D Schoeve, CSR, RDR, CRR, in and for the State of Texas, reported by computerized machine shorthand, at the Hilton Austin, 500 E 4th Street, Austin, Texas, pursuant to the Federal Rules of Civil Procedure and the provisions stated on the record or attached hereto

It is further agreed that Rule 30(b)(5) is waived by agreement of the parties

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Shane Ramirez, Videographer

THE COURT REPORTER:
Karen L D Schoeve, CRR, RDR, RSA

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REPORTER'S NOTE 1: Please be advised that an UNCERTIFIED ROUGH DRAFT version of this transcript exists. If you are in possession of said rough draft, please replace it immediately with this CERTIFIED FINAL TRANSCRIPT.

REPORTER'S NOTE 2: Quotation marks are used for clarity and do not necessarily reflect a direct quote.

EXHIBIT INDEX

EXHIBIT INDEX (Continued)

EXHIBIT INDEX (Continued)

EXHIBIT INDEX (Continued)

PROCEEDINGS

THE VIDEOGRAPHER: Here begins the deposition of Ellen Blair Smith, Ph.D.

THE WITNESS: No, M.D.

THE VIDEOGRAPHER: M.D. Excuse me.

Today's date is January 9th, 2019. The time is 9:24 a m.

Will the court reporter please swear in the witness.

ELLEN BLAIR SMITH, M.D., having been first duly sworn to tell the truth, the whole truth, and nothing but the truth, so help her God, testified as follows:

EXAMINATION

BY MR. JAMES:

Q. Good morning, Dr. Smith.

A. Good morning.

Q. Is Dr. Smith the appropriate way to refer to you?

A. Sure.

Q. Okay. My name is Scott James. I'm counsel for J&J, and we met briefly before the deposition, correct?

A. Yes.

Q. Where are you currently employed, Dr. Smith?

A. I am a hospice medical director for Halcyon Home, LLC.

Q. And do you have a separate consulting business?

A. No.

Q. We're here to take your deposition today in the talc MDL.

Do you understand that?

A. I do.

Q. When were you first contacted about serving as an expert witness in the talc MDL?

A. I was contacted to look at the scientific data in January of 2017.

Q. When did you first agree to serve as an expert in the litigation?

A. In about August or September in 2017.

Q. Who contacted you?

A. Margaret Thompson.

Q. How many contacts have you had with Margaret Thompson between the first contact and today?

A. Enumerable.

Q. More than ten?

A. Yes.

Q. More than 20?

A. I would think so.

Q. All pertaining to this litigation?

A. No.

Q. Okay. How do you know Ms. Thompson?

A. I've known Dr. Thompson for almost 40 years.

Q. And how did you first meet Ms. Thompson?

A. I was a fellow in gynecologic oncology at Duke, and she was a senior resident at Duke. She's one year behind me in training.

Q. How many meetings have you had with Mrs. Thompson pertaining to this litigation?

A. I don't know. A lot.

Q. Same series of questions. More than ten?

A. Yes.

Q. Okay. More than 20?

A. Yes.

Q. And have those meetings occurred between the first contact about the litigation, which was January 2017, and today?

A. Yes.

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Q. More than 30 meetings?
A. Probably not that many.
Q. Can you estimate the amount of time that you have spent with Mrs. Thompson pertaining to the issues in this litigation?
A. No, I cannot.
Q. Have you met with any other counsel for plaintiffs in this litigation?
A. Leigh O'Dell and Cynthia Garber.
THE WITNESS: And Paula, I don't know your last name.
MS. BROWN: Brown.
Q. (BY MR. JAMES) Any other counsel besides the ones you just mentioned?
A. No.
Q. How much time would you -- have all the meetings with Mrs. O'Dell and Ms. Garber -- and I -- my apologies, Mrs. Brown, have any of those meetings been without the presence of Mrs. Thompson?
A. No.
Q. Has Ms. Thompson been present at all of your meetings pertaining to this litigation?
A. Yes.
Q. Dr. Smith, have you given a deposition

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before?
A. Yes.
Q. So you understand the ground rules, but I'll repeat just a couple of them to help us along the way today, okay?
A. Okay.
Q. So my questions will be verbal, and I ask that your answers be verbal as well so they can be recorded.
A. Yes.
Q. If you need a break at any time today, please just let me know, and we'll be happy to accommodate you.
A. Thank you.
Q. And if you don't understand one of my questions, please ask me to rephrase, or oftentimes, your counsel will ask that I rephrase as well. Okay?
A. Thank you.
MR. KLATT: And can I add that we have an agreement that an objection for one is good for all?
MS. O'DELL: Yes.
MR. KLATT: Okay. Fine.

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MR. JAMES: Thank you, Mr. Klatt.
Q. (BY MR. JAMES) Have you ever worked as an expert -- a paid expert in litigation before?
A. Yes.
Q. What -- what matters?
A. It was expert testimony as an expert on cervical cancer, in between 1996 and 1998, for a local obstetrician gynecologist here in Houston, and the case pertained to appropriate treatment of carcinoma in situ of the cervix, and the patient's informed consent for a hysterectomy.
Q. Were you serving as an expert for the physician?
A. I was on the defense side, yes, sir.
Q. Have you served as an expert in any other litigation other than the one you just mentioned and the talc MDL?
A. No.
Q. How many prior depositions have you given?
A. Maybe five. I was -- I've been treating physician in several litigations, not an expert, just fact.
Q. Were you deposed in the -- as an expert in the litigation that you just discussed with us?

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A. The -- I was --
MS. O'DELL: Object to the form.
MR. JAMES: Sure.
MS. O'DELL: Just make sure . . .
Q. (BY MR. JAMES) So you mentioned that you served as an expert one time in one --
A. Right.
Q. -- prior case, correct?
A. Correct.
Q. Were you deposed in that case?
A. Yes.
Q. Were the other -- all of the other depositions taken in your capacity as a treating physician?
A. Yes.
Q. Have you been a defendant in any of those cases?
A. No.
Q. Are there any other depositions, other than the ones that we've just discussed, that you have given during your lifetime?
A. I gave a deposition -- oh, I gave a testimony and a deposition once as -- I don't exactly know what I was. I'm -- fact, and as a

patient at a hospital.
Q. Were you a defendant in that case?
A. No.
Q. For this case, for the talc MDL, turning back to the talc MDL, where do the fees that you receive in this litigation, where do those fees go to?
A. You mean come from?
Q. Do you take -- do you receive those fees personally?
A. Yes, I receive them personally.
Q. You are currently employed, as we discussed, correct?
A. Yes.
Q. Do you have any other sources of income besides the expert work that you're engaged in now and your current role for the hospice facility?
A. I have several personal annuities.
Q. Any other sources of income --
A. No.
Q. -- besides personal investments?
A. No.
Q. And you're charging $600 per hour in this litigation, correct?

A. I am.
Q. Is that a standard rate regardless of the sort of work you're performing?
A. In this MDL?
Q. Yes.
A. Yes.
Q. Yes, Doctor.
A. Yes.
Q. Can you quantify for us the number of hours you have spent working as an expert in this litigation?
A. I -- I don't have it off the top of my head, but I know they have very clear time records.
Q. Have you to date invoiced -- have you invoiced for all of the time that you've spent in the litigation to date?
A. No.
Q. Where do your invoices carry you through?
A. December 31st. I have -- there is an invoice that I submitted December 31st that's not been paid yet. But I'm through the end of 2018.
Q. And you'll be submitting an additional invoice for the time that you've spent in January, correct?

A. Correct.
MR. JAMES: And counsel mentioned before the deposition that they have brought with them copies of the invoices in litigation.
Could I have those, please.
MS. O'DELL: Sure.
MR. JAMES: Thank you.
MS. O'DELL: I'm missing a last invoice. I'll get it to you on the break.
MR. JAMES: Okay.
And I'm gonna hand what counsel has -- I'm gonna mark what counsel has handed me, the set of invoices, as Exhibit Number 1.
(Deposition Exhibit 1 marked for identification.)
Q. (BY MR. JAMES) And, again, Dr. Smith, these set of invoices that I was just handed will reflect the time that you've spent in this litigation through the end of December 2018, correct?
A. When you get the last one, yes, it will.
Q. Understood.
And then we get an additional invoice for January, correct?

A. Correct.
Q. How much time have you spent in January on this litigation?
MS. O'DELL: Just give your best estimate, if you don't . . .
A. 20. 15 to 20.
Q. (BY MR. JAMES) Can you break that time down for me, as far as what you've been doing during the month of January?
Has it been preparing for the deposition, reviewing --
A. Yes.
Q. -- articles?
I'm sorry. I --
A. Sorry.
Q. -- didn't finish the question --
A. I'm sorry.
Q. -- so let me rephrase it.
Has all the time that you've spent in January been preparing for the deposition?
A. Yes.
Q. For the total time that you've spent as work for -- strike that.
For the total time you've spent

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working in this litigation as an expert, can you give me a rough breakdown about the amount of time you've spent reviewing literature, reviewing company documents, and meeting with plaintiffs' counsel?
A. The vast majority of time has -- can I do it in percentages?
Q. That'd -- that would be fine.
A. Okay. I would say 75 percent is reviewing medical literature, 20 percent is meeting with -- maybe less than that. 15 percent is -- no. 20 percent is meeting with plaintiffs' attorneys, and the remainder is reviewing other documents.
Q. When you say "other documents," are you referring to company docket -- company documents and litigation materials you've been provided?
A. Yes.
Q. Have you discussed your involvement in this litigation with any of the other experts for the plaintiffs in the talc MDL?
A. No.
Q. And let me ask specifically about a few of the experts, if I may.
Have you discussed this litigation at all with Alan Campion?

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A. In terms of, "What are you doing?" "I'm reading articles," that kind of discussion.
In terms of when he was going to -- certainly in terms of when he was going out of town to do experiments, that kind of discussion.
But I did give him an article once that I didn't understand some of the technology in it. And I asked him if he understood it, to read it and see if he could explain to me, and he couldn't. So I guess that's talking about too.
Q. Do you recall the article in question?
A. It was a lab study. I think it was Lee.
Q. Did you discuss any other studies with Alan Campion?
A. I don't believe so.
Q. Have you discussed the substance of Campion's opinions with him?
A. No.
Q. What is your relationship with Alan Campion?
A. He's my husband.
Q. I understand.
Did Ms. Thompson first contact you or

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Mr. Campion about the litigation?
A. Me.
Q. And before you were retained as a litigation, did Ms. -- Ms. Thompson share with you any information about the litigation?
MS. O'DELL: Object to the form.
A. I'm not sure I understand that question.
Q. (BY MR. JAMES) What were the nature of the discussions before you were retained in this litigation with Ms. Thompson?
A. She informed me that she was involved in --
MS. O'DELL: Let's stop you right there. Dr. Smith, in terms of -- should have been quicker on my objection.
In terms of discussions with kind of like Dr. Thompson, those are -- those discussions are protected by the work prod- -- product privilege, so I'm gonna instruct you not to answer about any discussions that you had with the lawyers for the plaintiffs.
MR. JAMES: And that's -- just so I'm clear, that's regardless of whether the discussions were before she was retained or after she was

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retained?
MS. O'DELL: I think, in terms of the litigation when she billed for the time regarding those discussions, those are privileged. And -- and I believe if you'll look at the invoices, Dr. Smith has billed for all the time during which she's discussed the litigation.
Q. (BY MR. JAMES) Did -- did you recommend to Mrs. Thompson that she also reach out to your husband?
A. Yes.
Q. And why did you do that?
A. Leigh O'Dell said that --
THE WITNESS: Oh, is that work product?
MS. O'DELL: It is, but you can -- just to the degree I -- I made a suggestion to you, but don't go any further than that. Go ahead.
A. Yeah. Leigh O'Dell told me that the defense had recommended evaluation of particles by Raman spectroscopy.
And I said, "Too bad we don't know anybody who does that."
And Leigh and Dr. Thompson both said,

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"Yeah, it's too bad."
And I said, "My husband does that." I thought they knew.
MS. O'DELL: That's the extent of any disclosure, again, of communications with counsel.
THE WITNESS: Okay.
Q. (BY MR. JAMES) Did you refer Ms. Thompson to any of the other experts who were working on the MDL?
A. I did not.
Q. Do you understand that there are a number of experts that are working on the MDL for the plaintiffs that are located in Austin?
A. I know of one -- oh, I guess two. My husband is one of them.
Q. Other than your husband --
A. Yeah.
Q. -- do you know of any other experts who are located in Austin?
A. One, yes.
Q. And who is that?
A. Judy Wolf.
Q. And do you know Dr. Wolf?
A. Yes, I do.

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Q. Do you know here -- did you know her before this litigation?
A. Oh, yes.
Q. Did you refer Ms. Thompson to her for this litigation?
A. I did not.
Q. Do you know if Ms. Thompson contacted you or -- or Dr. Wolf first?
A. I believe I was contacted first.
Q. Have you had any discussions with Dr. Wolf about this litigation?
A. No.
Q. Have you had discussions with any of the other plaintiffs' experts about this litigation besides Alan Campion?
A. No.
Q. Are you familiar with a Dr. Clarke-Pearson?
A. Very well.
Q. Have you had any discussions with Dr. Clarke-Pearson about the litigation?
A. No.
Q. Have you exchanged any e-mails with any of the experts, including your husband about this

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litigation?
A. No.
Q. Have you exchanged any other writings or written materials about this litigation with any of the other experts in this litigation?
A. No.
Q. How long have you known Dr. Wolf, did you say?
A. Maybe 20 years.
Q. Did you reach out to her and encourage her involvement in litigation?
A. I did not.
Q. Did she reach out to you to encourage your involvement --
A. She did not.
Q. -- in litigation?
THE COURT REPORTER: Doctor, let him finish his whole question, please.
THE WITNESS: Yes, ma'am. I'm sorry.
Q. (BY MR. JAMES) Have you ever authored any publications concerning talc?
A. No, sir.
Q. Have you ever authored any publications concerning talc and ovarian cancer?

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A. No, sir.
Q. Have you ever authored any publications concerning asbestos?
A. No, sir.
Q. Have you ever published a talc or asbestos or risk factors for ovarian cancer?
A. No.
Q. Have you ever conducted any studies that pertain to the issues addressed in your report?
MS. O'DELL: Object to the form.
A. I am --
THE WITNESS: Can I answer it?
MS. O'DELL: Yes.
A. I am --
Q. (BY MR. JAMES) May I just rephrase?
A. Sure.
Q. Have you ever conducted any studies pertaining to the allegation that talc causes ovarian cancer?
A. No.
Q. Do you -- are you working on any articles that pertain to the issues in this litigation that you consider works in progress?
A. No.

Q. Do you have any plans to author or contribute to any articles that pertain to the issues in this litigation?
A. No.
Q. Have you submitted the substance or any -- any substance in your report to a journal for peer review?
A. No.
Q. Have you made any internet postings, blog postings, or other social media postings about the issues in this litigation?
A. No.
Q. Have you ever given any presentations, speeches, or lectures concerning talc and ovarian cancer?
A. No.
Q. The same question for asbestos and ovarian cancer.
A. No.
Q. Have you ever given any interviews or made any public statements concerning talc?
A. No.
Q. Concerning talc or ovarian cancer?
A. No.

Q. And concerning asbestos and ovarian cancer?
A. No.
Q. Have you ever counseled patients on risk factors for ovarian cancer?
A. Yes.
Q. What risk factors have you counseled your patients on?
A. Predominantly BRCA, Fanconi anemia pathway risk factors.
Q. And when you say "predominantly," are there any other risk factors for ovarian cancer that you've counseled your patients on?
A. No.
Q. Have you ever told a patient that talcum powder products was the cause or were the cause of their ovarian cancers?
A. No.
Q. Have you ever told a patient that talcum powder products was likely the cause of their ovarian cancer?
A. No.
Q. Have you ever asked any of your patients about their usage of talcum powder products?

A. Not to my recall.
Q. Have you ever asked your patients about their usage of talcum powder products in taking their medical histories?
A. No.
Q. And same question: Have you asked -- it's not the same question. Let me strike that.
Have you ever asked your patients about their exposure to asbestos in the course of taking their medical histories?
A. No.
Q. Have you discussed the opinions that you've rendered in your report concerning talc and ovarian cancer with any of your patients?
A. No.
Q. And have you discussed with any of your patients the opinions that you've rendered in your report concerning asbestos or other alleged constituents of talcum powder products?
A. No.
Q. Have you ever told any of your patients to stop using talcum powder products?
A. No.
Q. Have you ever cautioned any of your

patients about using talcum powder products?
A. No.
Q. Have you ever evaluated the personal risk of a patient for developing ovarian cancer based upon their history of usage of talcum powder products?
A. No.
Q. Have you ever recommended risk-reducing surgery on the basis of any of your patients' prior usage of talcum powder products?
A. No.
Q. Are you aware of any physicians who recommend risk-reducing surgery for patients with a history of usage of talcum powder products?
A. There is a published paper using use of talcum powder as one of the risk factors for doing oophorectomy and benign disease, but I didn't write that paper.
Q. Let me ask the question again. Just make sure I said it correctly.
A. Okay.
Q. Are you aware of any physicians that you know that recommend risk-reducing surgery to patients who have prior -- a history of usage of

talcum powder products?
A. No.
MS. O'DELL: Object to the form. I think the question, Mr. James, is just a little unclear. When you say "you know," are you talking about know of, know personally --
MR. JAMES: Sure.
MS. O'DELL: -- in the community? I mean --
MR. JAMES: Sure. I'll rephrase.
Q. (BY MR. JAMES) Do you know any physicians with whom you have a professional relationship who recommend risk-reducing surgery for patients who have a prior history of usage of talcum powder products?
A. No.
Q. You mentioned a paper in the course of -- of this line of questioning.
Do you recall the name of the paper that you're referring to?
A. The first author, it starts with a V, V-i-t. And the third author is Cramer. And it's some --
Q. Did you say V-i-d, Doctor? I'm sorry.

A. V as in Valentine. V- -- I can't spell the name. I can't remember the first name.
The third author is Daniel Cramer, and it was published in 2011 or 2013, and it's -- it's a paper about a risk scoring system to recommend oophorectomy in women who are undergoing hysterectomy, trying to establish their risk of ovarian cancer. One of such factors is talcum powder use.
Q. And do you recall if that paper recommends that physicians recommend to their patients risk-reducing surgery if they have prior history of talcum powder product usage?
A. That is not an exclusive factor in that risk assessment system.
Q. Are you aware of any medical or scientific organization that has recommended risk-reducing surgery for patients who report prior usage of talcum powder products?
MS. O'DELL: Object to the form.
A. I am not.
Q. (BY MR. JAMES) Do you understand that Dr. Cramer is a paid litigation expert for the plaintiffs?

A. I understand that.
Q. And Dr. Cramer is one of the authors that you identified as an author on the paper that you were just discussing, correct?
A. Correct.
Q. Have you ever recommended increased screening or monitoring for your patients for ovarian cancer based on their prior usage of talcum powder products?
A. No, I have not.
Q. Are you aware of any physicians with whom you have a professional relationship who do this?
A. No.
Q. Have you ever recommended to any doctors that you know professionally to tell their patients to stop using talcum powder products?
A. Yes.
Q. Okay. Who is that?
A. Which doctors I've recommended that to?
Q. Yes, Doctor.
A. Well, I didn't tell them to do it. I told them my concerns about talc, but I thought it was implicit in expressing my concerns that they would counsel their patients. I didn't tell -- I didn't

tell the doctors to do a lot of things.
Q. Understood.
A. Okay.
Q. And can you identify any of the doctors with whom you've had those conversations?
A. Yes.
Q. And please identify them.
A. Karen Swenson, Michael Breen, Anna Lozano.
Q. And are those physicians that you know here in the Austin community?
A. Yes.
Q. Are there any other physicians with whom you've discussed your concerns of talcum powder products?
A. Mark Crozier is a GYN, gynecologist, but he's no longer practicing. He's retired.
Q. And do you know if the three physicians that you've just identified do now indeed counsel their patients about talcum powder products?
A. I do not know.
Q. Did you have those conversations with those three physicians before your retention in the litigation or after?
A. After.

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Q. Have you recommended to those three physicians or any other physicians that they recommend to their patients risk-reducing surgery if they have prior usage of talcum powder products?
A. No.
Q. Have you suggested to those three physicians or any other physicians that they follow some sort of increased monitoring or screening of patients based upon prior usage of talcum powder products?
A. No.
Q. I'm going to hand you a copy of the deposition notice, which is why we're all here today. And I'm gonna mark that as Exhibit Number 2.
(Deposition Exhibit 2 marked for identification.)
MS. O'DELL: Thanks, Scott.
MR. JAMES: Yeah.
BY MS. O'DELL: We previously served objections, and I'll just -- to certain document requests that are contained in the notice, and I would just reassert those now for the record.
MR. JAMES: Understood.
Q. (BY MR. JAMES) Dr. Smith, have you seen a

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copy of this deposition notice before?
A. Yes.
Q. And when were you pro- -- when were you provided a copy?
A. Saturday or Sunday -- this past Saturday or Sunday.
Q. And I understand that you and your counsel have brought with you to today's deposition a number of materials, correct?
A. Correct.
Q. And we've discussed and marked the invoices already. And so Ms. O'Dell is looking toward a table with other materials that I'll describe.
Are those the materials that you've brought with you that respond to the deposition notice?
A. Yes, sir.
Q. And Ms. O'Dell and I discussed prior to the deposition, but the materials that you've brought with your -- with you today to today's deposition are your materials considered in your references, correct?
A. Correct.

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Q. And you've also brought with you a separate pile of -- a smaller set of studies or literature that you have included some notes on, correct?
A. Correct.
Q. And without getting up and moving around right now, I would like to mark the subset pile as Exhibit Number 3.
MR. JAMES: Okay, Leigh?
MS. O'DELL: Yeah.
(Deposition Exhibit 3 marked for identification.)
Q. (BY MR. JAMES) And we'll apply the sticker at the break. Okay?
Dr. Smith, are there any other materials that -- that you've brought with you today that we have not discussed?
A. No.
Q. Are there any other materials that -- that having looked back at this deposition notice today, that you can think of that are responsive that you have not brought with you?
A. No.
MS. O'DELL: I say that subject to the

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objections.
MR. JAMES: Understood.
Q. (BY MR. JAMES) Okay. I'm going to hand you, Dr. Smith, what you have in front of you already, and I'm going to mark as Exhibit Number 4 a copy of the report that you authored in this litigation.
(Deposition Exhibit 4 marked for identification.)
Q. (BY MR. JAMES) And, Dr. Smith, I'm gonna hand you the -- the stickered copy, but I understand that you have an identical copy in front of you, correct?
A. Correct.
Q. And if throughout the deposition today you prefer to flip it in the loose-leaf binder, that's fine as well. Okay?
A. Okay. May I --
MS. O'DELL: Just leave it there.
A. May I point out a couple of corrections for that, because I've only recently --
MS. O'DELL: Dr. Smith, you certainly may, but let him ask you the questions.
Q. (BY MR. JAMES) Yeah. I'm actually going

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to ask you that question, so you'll have a chance to.
A. Okay.
MR. JAMES: And if counsel, down the line throughout the day, has any requests of copies of anything I'm handing out, just let me know. I have some.
Q. (BY MR. JAMES) Okay. Dr. Smith, you would agree that the report that I've handed you and marked as Exhibit Number 4 defines the scope of your opinions in this litigation --
A. Yes.
Q. -- correct?
MS. O'DELL: Object to the form. Excuse me. I was a little off the mark.
MR. JAMES: Okay.
Q. (BY MR. JAMES) Dr. Smith, do you have any changes to this report that you'd like to make today?
A. Yes.
Q. And what are those changes?
A. There is deficient of second parenthesis, and I'm trying to figure out where it is in here. Let me go to more substantive things.

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On page 7 where it says, "A Cancer Genome," second paragraph. Do you know where I am, page 7, second paragraph?
Q. Yes. Yes, Doctor.
A. It should be "The Cancer Genome Atlas," not "A Cancer Genome Atlas."
Do you want me to mark it on here?
Q. It's fine.
A. Okay. And then on the chart labeled on Exhibit B the single gene studies, on the second page, the back page under Wu, 2015, the fourth column, 1.56.
Are you with me?
Q. Yes, Doctor.
A. That 1.56 and 1.77 are inverted. The 1.77 should go with Hispanics as is the confidence intervals. The 1.56 should go with African-Americans, as does that conference intervals, just a transposition.
Q. Are there any other changes to the report that you'd like to make today?
A. Well, I haven't found the parentheses yet, but you'll figure it out when you see it.
Q. Okay. Dr. Smith, did you write this

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report?
A. I did.
Q. Is all of the wording in this report your wording?
A. Yes.
Q. Did you consult with Dr. Wolf in writing your report?
A. I did not.
Q. Did you meet with Dr. Wolf in writing your report?
A. I did not.
Q. I'm gonna mark as Exhibit Number 5 a copy of Dr. Wolf's report in this litigation.
(Deposition Exhibit 5 marked for identification.)
Q. (BY MR. JAMES) Dr. Smith, have you seen this report before?
A. No.
MR. JAMES: I apologize to -- to counsel and to you, Dr. Smith. I have a bad back which prevents me from leaning too --
A. That's okay.
Q. -- further -- too far forward.
Dr. Smith, at first I'd like you to

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pull out your report.
A. Um-hum.
Q. And I'd like you to turn to page 16 of your report, please.
A. (Complied.) Um-hum.
Q. And if you look down at the one, two, three, fourth full paragraph.
A. Um-hum.
Q. Actually, it's the -- when I say "full," it's the third full paragraph. It's the paragraph that starts with "In my opinion."
A. Um-hum.
Q. Do you see that paragraph?
A. Um-hum.
Q. If you look at that last sentence of that paragraph -- I'm gonna read and make sure I read it correctly.
It says, quote, "All of the cohort studies are limited by failure to obtain complete information, lack of power, selection bias, and short follow-up," close quotes.
Did I read that correctly?
A. Yes.
Q. And if you could turn, then, to Dr. Wolf's

report, please.
A. What page?
Q. And I'm looking at page 8 of Dr. Wolf's report. And it's second full paragraph, so it's the second section on that page. I'm gonna quote a page of Dr. Wolf's report here.
A. (Complied.) Um-hum.
Q. Okay. It's the sentence that starts with the word "All."
Do you see where I am?
A. Um-hum.
Q. Okay. It says, quote, "All of the cohort study are limited by lack of power, failure to make the appropriate queries, selection bias, and short follow-up," close quote.
A. Um-hum.
Q. Do you see that section that I read?
A. I do.
Q. And did I read that correctly?
A. You did.
Q. Do you agree that those two sentences are remarkably similar?
A. They are similar.
Q. And is your testimony that the wording in

your report is purely your wording?
A. It is.
Q. All right. If you could turn back to your report, please, Dr. Smith, on page 16.
A. (Complied.) I'm on 16. Okay.
Q. Okay. And if we look down, it's the -- it's the paragraph below the paragraph that we just read. It starts with the "When looking" phrase.
Do you see --
A. Um-hum.
Q. -- where I am?
A. Um-hum.
Q. Okay. And if you look at that paragraph, Dr. Smith, on page 16, that full paragraph.
A. Um-hum.
Q. If you could read that to yourself right now, please.
A. Okay. (Examined exhibit.)
Q. And it's the paragraph that starts with the phrase "When looking at epidemiological studies."
A. Um-hum.
Q. And have you had a chance to read that?
A. I have.

Q. Okay. And if you look at page -- if you can turn to Dr. Wolf's report, please.
A. Um-hum.
Q. Okay. If you turn to Dr. Wolf's report on page 8 --
A. Um-hum.
Q. -- it's the bottom paragraph.
A. (Complied.)
Q. And Dr. Wolf starts a paragraph with the same phraseology. She says, quote, "When looking at epidemiological studies."
Do you see where I'm reading?
A. Um-hum.
Q. And have you had a chance to review her paragraph there?
MS. O'DELL: Object to the form.
A. (Examined exhibit.) I do.
Q. (BY MR. JAMES) Okay. Would you agree that those two paragraphs are remarkably similar?
A. I'm not --
MS. O'DELL: Object to the form.
A. -- quite through that.
Q. (BY MR. JAMES) Please take your time. I'm sorry.

A. (Examined exhibit.) They're similar. I think it's because we looked at the same data.
Q. And, Dr. Smith, within that paragraph, I'm gonna call your attention to two specific sentences.
So I'm looking back at your report, Dr. Smith, and you say, quote -- in your report, quote, "Recall and confounding bias in case-control studies appear to have minimal impact."
A. Um-hum.
Q. "(Penninkilampi and Eslick 2018;" --
A. Um-hum.
Q. -- "Langseth 2008)."
A. Um-hum.
Q. "There appears to be no significant publication bias."
A. Um-hum.
Q. "(Berge, 2017;" --
A. Um-hum.
Q. -- "Penninkilampi 2018)," close --
A. Um-hum.
Q. -- quote.
Did I read that correctly?
A. You did.
Q. And do you see that in Dr. Wolf's report

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she has those exact same sentences verbatim?
A. Yes.
Q. And, again, is your testimony that the wording in this report is your wording?
A. It is my wording.
Q. Okay. Dr. Smith, if you could look at page 7 of your report. If you look at the bottom paragraph, about halfway down through that paragraph, Dr. Smith, you state the following --
A. Page 7?
Q. Yes, Dr. Smith.
A. Okay.
Q. It's the last paragraph on that page, right above the visuals.
A. (Complied.) Um-hum.
Q. Do you see the sentence that starts with the word "binding"? "Binding of BCDX2 or CX3," it's a Holliday Junction.
Do you see where I'm reading?
A. Um-hum.
Q. And if I kept rea- -- if I keep reading, that sentence ends with a citation to the Compton 2010 study.
Do you see that?

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A. Um-hum.
Q. Is that wording in that sentence your wording or is that quoted from the article?
A. It's quoted from the article, I believe. By -- that's why it's referenced.
Q. Oh, understood. Is that what you were referring to earlier as something that was missing a quote?
A. No. No, it's not a quo- -- I -- what I was referring to is there's missing a back half of a parenthesis in the text.
Q. Do you agree that if you're quoting verbatim from one of the sources that you cite that you should include quotations in your report?
MS. O'DELL: Object to the form.
A. I'm not sure that's necessary in a scientific paper. I think the importance is it's cited.
Q. (BY MR. JAMES) You submitted articles to peer-reviewed journals before, correct?
A. I have.
Q. And your understanding is that if -- if something is cited without quotes that's standard?
MS. O'DELL: Object to the form.

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A. I think it's allowable.
Q. (BY MR. JAMES) Are there any other passages in your report that you can recall that you would have written verbatim but not quoted? Excuse me, strike that.
Are there any other passages in your report that you have cited to a source and included text verbatim from that source --
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) -- that you did not put in quotations?
MS. O'DELL: Excuse me. Object to the form.
A. I don't remember any.
Q. (BY MR. JAMES) Okay. Dr. Smith, with your expert report you produced a copy of your CV.
A. Yes.
Q. Correct?
A. Yes.
Q. Since providing your counsel with a copy of the CV that was then provided to me, have there been any changes to your CV?
A. No.
Q. I'm gonna mark the CV, then, that was

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produced to the defendants as Exhibit Number 6.
(Deposition Exhibit 6 marked for identification.)
Q. (BY MR. JAMES) I'm gonna hand you a copy, Dr. Smith. Sorry again for the --
A. That's okay.
Q. -- throwing.
MS. O'DELL: If you just hand them to me, I'll be glad to hand them over.
MR. JAMES: Thank you so much.
Q. (BY MR. JAMES) And, again, Dr. Smith, this is your current CV that you're looking at, is Exhibit Number 6?
A. (Examined exhibit.) Yes, it is.
Q. Thank you. Okay.
In your report, Dr. Smith, you describe the methodology that you've conducted to collect the materials that you reviewed, correct?
A. Correct.
Q. And I see you're still looking at your CV, so I don't intend to rush you.
A. That's okay. It's fine.
Q. And so I am -- I'm not gonna ask you any further questions about the CV if you want to set

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that aside.
A. Oh, okay. (Complied.) Okay.
Q. I'm gonna turn to your report now.
A. Okay.
MS. O'DELL: Yeah, just -- we can maybe stack -- thank you.
Q. (BY MR. JAMES) The searches that you ran to capture the materials that you reviewed for purposes of forming your litigation opinions, had you run those searches before being retained as an expert in this litigation?
A. No.
Q. Had you read any of the studies that you cite in your report before being retained in the litigation?
A. Yes.
Q. Is there a way for you to delineate which studies that you reviewed before your retention and which studies you reviewed after?
A. I know I'd seen Cramer 82.
Do you want me to go through my references list and try to identify which one I've seen before?
Q. Well, we understand that the reference

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list is -- is lengthy, correct?
A. It is.
Q. Do you think that you're looking for a handful of articles or a larger set of articles that you saw before your retention?
A. I would say it's larger than that on these references, yes.
Q. Okay. And so rather than us take the time to do that now, Dr. Smith, sitting here today, is there any way for you to delineate or define which ones you reviewed before being retained?
A. Do I --
MS. O'DELL: Object to the -- excuse me. Object to the form.
I think she just -- she's willing to do that, if you want her to go through the list, but --
A. Or I can put a check on them, if you want.
Q. (BY MR. JAMES) Let's not do that right now. How about that?
A. Okay.
Q. And then we'll think about how we approach that.
Did plaintiffs' counsel provide you

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any of the studies that are listed in your references or materials considered lists?
A. Yes.
Q. Is there any way for you to delineate which studies were provided to you by plaintiffs' counsel and which ones that you found on your own?
A. Frequently I would provide them an abstract asking for full text, so that happened a lot. There were some that they sent to me as these studies were coming out in e-Pubs, e-publication, prior to print publication. I could go through, and, again, try to mark those.
Q. Would you have in your possession records that would help you come up with a list of what was provided to you versus what you found on your own?
A. No, but, like, I know that things that came out in '17 and '18 usually they got before I did.
Q. And those are the prepub versions you were just mentioning?
A. Right. They usually weren't prepublication. They were usually peer --
Q. You said e-Pub?
A. Yeah. e-Pub.

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Q. My apologies.
A. Yeah, that didn't have a citation, right.
Q. In your report under the Methodology section, Dr. Smith, you say that you, "Began with a comprehensive review of the medical literature," and then you use the phraseology, "ON many topics."
Is that -- do you recall using that phraseology? It's at page 2.
MS. O'DELL: Object to the form.
A. (Examined exhibit.) I'm looking for -- it says --
Q. (BY MR. JAMES) It's the first sentence, Doctor -- it's the second sentence, Dr. Smith.
A. Then I read many of the references of the articles cited in those papers. I didn't see many topics.
Q. Sure. So in the second sentence -- and I -- my questioning is probably unnecessarily confusing.
But in the second sentence under Methodology, you say that you relied on PubMed searches on many topics.
Do you see that?
A. Oh, that. Okay. Oh, that was the second

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sentence. Sorry, I was off by one. Yes.
Q. And -- and then later on you just mentioned, Dr. Smith, you note in this paragraph that you also looked at the references of the articles --
A. Right.
Q. -- and conducted some additional Google searching, correct?
A. Correct.
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) When you refer to the "many topics" there, can you define what many topics you are referring to?
A. Sometimes you find different -- when you're using a search engine, even in PubMed, if you put in -- put it in one way and it looks like talc and ovarian cancer, then you put it in ovarian cancer, and talc you may get deferences on how you go back. Inflammation in carcinogenesis. Then you look at inflammation and ovarian cancer.
So just, if you word it differently, you can pick up different references, and they come out in different order sometimes. So it's -- when you're looking for everything, you need to, kind of,

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mix it up and say it different ways to try to find all the articles.
Q. For every topic that you looked at, did you conduct a comprehensive review for the underlying scientific and medical literature?
A. Yes.
Q. So every topic that you've addressed in your paper was a critical component of your meth- -- methodology to conduct a comprehensive review and capture all of the relevant and scientific -- the relevant scientific and medical literature?
A. That --
MS. O'DELL: Object to the form. Give me --
A. That was --
MS. O'DELL: Excuse me. Just give me just a second, and I'll get my obj- -- object to the form. Thank you.
A. That was my attempt.
Q. (BY MR. JAMES) Do you agree that prior to offering expert opinions on particular topics an expert should be expected to conduct a con- -- comprehensive review of the scientific and medical literature on that topic?

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MS. O'DELL: Object to the form.
A. I would agree with that.
Q. (BY MR. JAMES) You agree that --
THE WITNESS: Am I supposed to wait, Laurel [sic]?
MS. O'DELL: Just give me just a -- just a second.
THE WITNESS: Okay.
MS. O'DELL: I'll try to be quicker on the draw.
THE WITNESS: Okay.
Q. (BY MR. JAMES) Do you agree that doing that is a fundamental first step to your methodology?
A. I do.
Q. Would you agree that any opinion formed on an incomplete review of the relevant scientific and medical literature on a particular topic would be unreliable?
MS. O'DELL: Object to the form.
A. Not necessarily. Not necessarily.
Q. (BY MR. JAMES) And why do you say that?
A. I mean, if you miss -- if a person misses one article but has a substantial amount of the

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information required, they can reach the right conclusion and have not read one article.
Q. Then do you -- again, do you agree that the methodology to opine on a particular topic should start with the intent to capture the relevant scientific and medical literature on that topic?
MS. O'DELL: Object to the form.
A. I agree.
Q. (BY MR. JAMES) Do you believe that you conducted a comprehensive review in the manner that we just described on the topic of heavy metals and ovarian cancer?
MS. O'DELL: Object to the form.
A. No.
Q. (BY MR. JAMES) Do you believe that you followed the methodology that we just described on the topic of fragrances and ovarian cancer?
MS. O'DELL: Object to the form.
A. I read a limited amount of material on fragrances.
Q. (BY MR. JAMES) And so my question remains.
Do you agree -- or do you believe that you followed the methodology that we just described

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in forming your opinions on fragrances and ovarian cancer?
A. No.
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) Do you believe that you followed the methodology that we just described in forming your opinions on asbestos and ovarian cancer?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) Do you believe that you followed the methodology that we just described on the issue of, quote, "fibrous talc," close quote, and ovarian cancer?
A. Yes.
MS. O'DELL: Object to the form.
Give me just a second, Doctor. Thank you.
Q. (BY MR. JAMES) Dr. Smith, can you explain to me the difference between the reference list attached to your report and the -- what I refer to as the materials considered list attached to your report as part of Exhibit C?
Do you understand that there are two

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different lists?
A. Yes, I do.
Q. Okay. Can you explain to me the difference between those two lists, the significance of why they're placed on one list versus the other?
A. If I used a reference in my paper, it is on my reference list.
The larger reference list, I believe, is what's called a reliance list that aggregates all the references that all the experts that are involved in this litigation had as one master list of reference for the whole litigation.
Does that make sense?
Q. Was that a list that you created, the materials considered list?
A. The reliance list, the last one?
Q. Yes, Doctor.
A. I did not create that.
Q. Did you review all of the sources listed on that list?
A. There are sources on there that I have not reviewed.
Q. Is there any way for you to delineate which sources you reviewed on the -- what you're

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referring to as the reliance list and which sources you did not review?
A. I'd have to go through it one by one. I'd be glad to.
Q. Yeah. I think that we're time limited today, so I ask that we not do that at this time.
A. Okay.
Q. Are there materials that you reviewed and that you concluded were not relevant to your opinion cited on the reliance list but not on the reference list?
MS. O'DELL: Objection to form.
A. I think that -- so are we calling the Exhibit C a reliance list --
Q. (BY MR. JAMES) I think, Doctor --
A. -- and my --
Q. I was trying to use your terminology, but it's -- I'll just --
A. Okay.
Q. -- to be clearer, I'll ask the question with Exhibit C.
A. Okay.
Q. Are there materials contained on Exhibit C that you reviewed but did not cite to or discuss in

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the text of your report?
MS. O'DELL: If you understand the question, Doctor. If you're confused about the question, then I'm sure counsel will be glad to rephrase it. Because with the terminology, this is getting -- it is a little confusing.
A. Could you clarify that --
Q. (BY MR. JAMES) Sure. I'll try to.
A. -- because I am a little confused.
Q. I'll try.
A. I'm sorry.
Q. That's okay.
Did you review materials cited on the Exhibit C that you concluded were not relevant to your opinions?
A. I can't recall anything.
Q. In your report, you make reference to looking at company documents, correct?
A. Correct.
Q. Did you affirmatively request those company documents or were those provided to you by counsel without you requesting those?
A. Those were provided to me without request.
Q. Did counsel -- sitting here today, do you

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recall the information or subject matter of the company documents that you reviewed?
A. Ummm . . .
MS. O'DELL: Object to the form.
If there's any confusion in the question, Doctor, just ask him to rephrase it. But if you understand the question, feel free to answer.
A. I believe that the -- there was a newspaper article about condoms and exclusion of talc products with condoms, that was a company document that I saw.
Q. (BY MR. JAMES) Did the company documents that you were provided by counsel inform your opinions in this case?
A. No -- well . . . No.
Q. When counsel provided you the company documents to review, did you ask for any additional company documents?
A. No.
Q. Did you ask for context to those company documents?
MS. O'DELL: Object- -- objection to form of the question.
You -- don't reveal any communications

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you've had with counsel about company documents, or any other thing, for that matter --
THE WITNESS: Okay.
MS. O'DELL: -- but in regard to this topic.
MR. JAMES: Well, I'm just asking what she's asked to see. So --
THE WITNESS: I haven't asked to --
MR. JAMES: -- I'm asking --
THE WITNESS: -- see anything.
MR. JAMES: Well, I'm sorry, Dr. Smith.
THE WITNESS: Sorry.
MR. JAMES: So if you feel like there's a way to rephrase my question, that's what I'm trying to get at.
MS. O'DELL: I think you asked -- I heard you ask a different question than asked --
MR. JAMES: Okay. Let me try again.
MS. O'DELL: -- than that. So just -- if you don't mind, rephrase it.
MR. JAMES: Understood.
Q. (BY MR. JAMES) After you were provided the company documents, did you ask if there were any

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additional documents that would provide context to the documents that you were initially provided?
A. I --
MS. O'DELL: Object to the form.
A. I don't believe so.
Q. (BY MR. JAMES) Did you ask if any defense witness had ever authored any testimony about the company documents you were provided?
MS. O'DELL: Excuse me, Doctor. Don't testify to any communications with counsel.
So if you -- you can ask her, did she ask a question. She can say yes. But in terms of the subject matter of the question, the content of that conversation, I'm gonna object and just instruct the witness not to answer.
Is that -- is that a fair distinction --
MR. JAMES: But you're allowing the witness to answer whether she asked for it, correct?
MS. O'DELL: I think I -- you asked that question and I allowed it.
MR. JAMES: Got it.
MS. O'DELL: But to the degree you've asked for what her questions were, what the

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discussion was, I think that is protected.
MR. JAMES: Got it.
Q. (BY MR. JAMES) So did you ask for any -- once you were provided the company documents that you were provided by counsel, did you ask whether the defense had ever offered any testimony or witnesses about the contents of those documents?
MS. O'DELL: Excuse me, Doctor. Don't answer that question.
That's the subject matter of the communication, and I'm not gonna allow her to answer those questions.
So don't answer the question.
Q. (BY MR. JAMES) Do you know if any defense witness has ever addressed the content of the company documents that you were provided by counsel?
MS. O'DELL: Object to the form.
A. I don't know that.
Q. (BY MR. JAMES) You would agree with me that if you were attempting as a scientist to form opinions on a particular topic you would want to be sure that you were provided both sides of the story, correct?
MS. O'DELL: Object to the form.

You may answer the question if you understand it, Doctor.
A. I think the scientific literature presents both sides of the story. That's how you factor it in, right? You usually don't call up individuals and ask them their opinion. Their published, peer-reviewed opinions are available in the literature.
Q. (BY MR. JAMES) Dr. Smith, in your report in discussing asbestos, you mentioned litigation reports authored by a Dr. Longo, correct?
A. Yes.
Q. Okay. So we were just talking about company documents --
A. But now --
Q. -- in the -- prior to the questioning, and I want to just make sure you know where I'm going.
You testified that the company documents did not inform your opinions, correct?
MS. O'DELL: Object to the form.
A. Yes. Perhaps you and I are talking about different things between company documents and litigation documents.
Q. (BY MR. JAMES) Sure. And I think -- fair

enough.
Let's just move on to the Longo requesting.
A. Okay.
Q. And with respect to asbestos, you looked at Longo litigation reports, correct?
A. I did.
Q. You understand those to be litigation materials, correct?
A. Yes.
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) Do you understand Longo -- Dr. Longo is a paid litigation expert, correct?
A. Yes.
Q. And you understand his reports are not peer-reviewed, correct?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) You understand that they're not published, correct?
A. Yes.
Q. Do you know if anyone on the defense side has addressed or responded to Dr. Longo's litigation reports?

A. I do not know that.
Q. And wouldn't you want to know that as a scientist before forming opinions upon Dr. Longo's reports?
MS. O'DELL: Object to the form.
A. I would be interested in that.
Q. (BY MR. JAMES) And counsel didn't provide that information to you, did they?
A. They did not.
MS. O'DELL: I would just object to the statement that somehow that question assumes, Counsel, that defense -- defendants in this case have served expert reports, which they have not. It's a little misleading, but . . .
Q. (BY MR. JAMES) You were looking at Dr. Longo's litigation reports from other cases.
Did you know that?
MS. O'DELL: Dr. Smith is not involved in other cases, so I'm not sure she would have information to know what's another case or what the present case. So to be fair --
MR. JAMES: Leigh, I've asked a fair question, and I think Dr. Smith is capable of answering it.

MS. O'DELL: I'm not sure that that's a fair question.
If you understand it --
MR. JAMES: Well, why don't you please state your objection and then let Dr. Smith answer, if you can.
MS. O'DELL: Object to the form.
MR. JAMES: Thank you.
A. Could you say it again? I got lost.
Q. (BY MR. JAMES) Sure. You've already agreed with me that the Longo reports that you've reviewed are litigation reports, correct?
A. Right.
Q. Okay. And your counsel just stated that the Longo litigation reports were not part of the MDL litigation.
MS. O'DELL: That's not what I said.
MR. JAMES: Okay.
Q. (BY MR. JAMES) Nevertheless, you have reviewed litigation reports from plaintiffs -- an expert that's paid by plaintiffs in this litigation, correct?
A. I have.
Q. You have also reviewed a litigation report

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prepared by a Dr. Crowley, correct?
A. Correct.
Q. And that pertains to fragrances, correct?
A. Correct.
Q. You understand Dr. Crowley's report is not peer-reviewed, correct?
A. Correct.
Q. You understand his report is not published in the medical literature, correct?
A. Correct.
Q. Did you review any of the other expert reports besides Dr. Crowley's report in this MDL?
MS. O'DELL: In addition to Dr. Longo.
MR. JAMES: Thank you.
Q. (BY MR. JAMES) In addition to Dr. Longo?
A. I don't think so.
MS. O'DELL: Hey, Scott, we've been going about an hour and 15 minutes or something close to that, hour and 10 minutes. Whenever it's a good place --
MR. JAMES: Another 5 to finish this line.
Is that good, Doctor?
THE WITNESS: Sure.

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MR. JAMES: Okay.
Q. (BY MR. JAMES) Dr. Smith, you also looked at -- or at least you listed, in your lists, you looked at the deposition of a Dr. Alice Blount, correct?
A. Oh, yes.
Q. Okay. Does that ring a bell?
A. Yes. But is she involved in this litigation?
Q. That was gonna be my question to you.
Did you know that Dr. Blount has testified as an expert for plaintiffs in the talc litigation?
A. In --
MS. O'DELL: Excuse me. Object to the form.
A. In this MDL?
Q. (BY MR. JAMES) In the talc litigation --
A. Oh, in the talc litigation, yes.
MS. O'DELL: Object to the form. I think it's a mischaracterization to say she's an expert, to my knowledge.
So you want to restate your question.
Q. (BY MR. JAMES) Do you know that

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Dr. Blount has been listed by plaintiffs in talc litigation as an expert for plaintiffs?
MS. O'DELL: Object to the form; misstates the testimony, as I understand it.
A. I know she's been deposed.
Q. (BY MR. JAMES) Did you review her testimony in full?
A. I -- I reviewed her paper, and I read her testimony fairly superficially.
Q. Do you know if the defense in the talc litigation has responded to or addressed Dr. Blount's testimony and article?
A. I do not know that.
Q. Wouldn't you like to know that?
MS. O'DELL: Object to the form.
A. Sure.
Q. (BY MR. JAMES) Is there a reason that you didn't consider the defenses' response to Dr. Blount's testimony and article?
MS. O'DELL: Object to the form of the question.
There have been no expert reports in -- by -- served by defendants in the MDL. That's an unfair question.

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A. I'm lost again. I'm sorry.
Q. (BY MR. JAMES) Sure. I understand.
You read Dr. Blount's testimony superficially is what you just testified to, correct?
A. Yes.
Q. You understand Dr. Blount testified in another case in the talc litigation, correct?
A. Yes.
Q. Do you know if the defendants responded to Dr. Blount's testimony and report in that case?
A. I do not know that.
Q. You've cited in your report a deposition exhibit from a Dr. John Hopkins.
Does that ring a bell?
A. It does.
Q. Okay. And you also cited a deposition exhibit from a Julie Pier.
Does that ring a bell?
A. It does.
Q. And why did you look at those two exhibits?
A. I looked at the identification in Pier on minerals and quantities, parts per million.

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I looked at the Hopkins', the identification of asbestos and asbestiform species in various ore and talcum powder products.
Q. Did you consider both of those exhibits relevant to the opinions that you formed concerning asbestos and ovarian cancer?
A. Yes.
Q. Did you -- do you know if the defense has addressed or responded to the information contained in those two deposition exhibits?
A. I --
MS. O'DELL: Object to the form.
A. I do not know.
Q. (BY MR. JAMES) Did you ask if the defendants have responded to the information contained in those exhibits?
MS. O'DELL: Object to the form.
A. I did --
MS. O'DELL: And I -- excuse me. And I would instruct you just-- he's asking you about what you talked about with your lawyers for the plaintiffs, and I would just instruct you not to answer that question, as I've instructed you on every other line of inquiry to that extent.

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I instructed her not to answer that.
A. I'm --
MR. JAMES: Understood.
A. -- not responding.
Q. (BY MR. JAMES) Yeah, understood.
Would you like to know if the defendants have responded to the information contained in the two deposition exhibits that you cited?
A. Yes, I would.
MR. JAMES: Is now good for a break?
MS. O'DELL: Sure.
MR. JAMES: Okay.
Thank you, Doctor.
THE VIDEOGRAPHER: Going off the record. The time is 10:34 a.m.
(A recess was taken from 10:34 a.m. to 10:53 a m.)
THE VIDEOGRAPHER: Back on the record. The time is 10:53 a m.
Q. (BY MR. JAMES) Okay. Dr. Smith, are we ready to proceed?
A. I am.
Q. Great.

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Dr. Smith, did you do any independent testing to support your opinions in this case?
A. I did not.
Q. Did you do any independent analysis or reanalysis of raw data to support your opinions?
A. I did not.
Q. On page 2 of your report, Dr. Smith, you conclude with a passage where you state that you have applied in this litigation, quote, "The same methodology and scientific rigor that I have used regularly in my professional career and clinical practice," closed quote.
Do you see that passage that I read?
A. Oh, yes. In the -- under Methodology?
Q. Yes, Doctor.
A. Yes.
Q. Did you see where I read?
A. Yes.
Q. Okay.
A. Yes.
Q. In your professional practice and your clinical practice, do you rely on litigation reports by paid experts?
MS. O'DELL: Object to the form.

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A. No.
Q. (BY MR. JAMES) Do you rely on unpublished data or unpublished testing as a clinician?
MS. O'DELL: Object to the form.
A. Occasionally, there is unpublished data that you may cite information from an author for the things that weren't in publication material. That -- that happens commonly with a lot of scientific reports.
Q. (BY MR. JAMES) As a clinician, have you ever relied on the type of litigation materials that you have reviewed in your capacity as an expert in this case?
MS. O'DELL: Object to the form; vague.
A. I don't think so.
Q. (BY MR. JAMES) As a clinician, in your daily practice or your professional practice, have you ever relied on deposition testimony of paid experts to form your opinions?
MS. O'DELL: Object to the form.
A. No.
Q. (BY MR. JAMES) Before being contacted by counsel in this case, had you formed an opinion as

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to any cause of ovarian cancer?
A. (No response.)
Q. And let me rephrase that --
A. Yes.
Q. -- because it's prob- -- it's phrased poorly.
Before being contacted about work in this litigation, had you reached the conclusion that there were any causes of ovarian cancer?
A. Yes.
Q. And what had you concluded before being contacted in the litigation about causes of ovarian cancer?
A. Well, I'm not sure that I understand how -- what do you mean "cause"?
Q. You understand that in the epidemiologic literature, the word "association" is used, correct?
A. Yes.
Q. And the word "cause" is used, correct?
A. Correct.
Q. In your clinical practice, if someone asked you what caused their ovarian cancer, would you know what they were asking you?
A. Yes.

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Q. By the word "cause"?
A. Yes.
Q. And so I don't mean for my question to be confusing. I'm -- what I'm asking you is if -- certainly in this litigation, you have offered the opinion in your report that in your opinion talc causes ovarian cancer, correct?
A. Correct.
Q. Did you form that opinion, that causation opinion, after being retained in this litigation?
A. After reviewing the literature.
Q. And after being retained; is that right?
A. Correct.
Q. And so my question to you, which I hope is simple, is that before you were contacted about work in this litigation, had you concluded that there was anything else out there that could be categorized as a cause of ovarian cancer?
A. Are you -- causation such as genetic predisposition?
Q. That would be one of them.
A. Okay. Yeah. Then we're on the same page.
Q. Okay. And so had -- had you concluded before your work in this litigation that genetics,

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loosely, could -- could be categorized as a cause of ovarian cancer?
A. Yes.
Q. Is there anything else that you had concluded before your work in this litigation that could be categorized as a cause of ovarian cancer?
A. Yes.
Q. What else?
A. Endometriosis.
Do you want more?
Q. Yes. If you could list any others.
A. Nulliparity, some data on obesity, mixed data on pelvic inflammatory disease, mixed data on smoking. That's what has come to the top of my head.
Q. And just to make sure that we're on the same page, my question at this point is still confined to the issue of cause.
And so of the items that you just mentioned before being retained in this litigation, had you concluded that obesity is a cause of ovarian cancer?
MS. O'DELL: Object to the form.
A. Mixed data on that. More pertaining to

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endometrioid cancers.
Q. (BY MR. JAMES) So you would -- did you hold the opinion before your work in this litigation that obesity was a cause of ovarian cancer?
MS. O'DELL: Object to the form.
A. Partially.
Q. (BY MR. JAMES) And when you say "partially," are you referring to the subtype?
A. Yes.
Q. And so of the i- -- the items that you did just mention to me, then, you do consider those to be -- you did consider those to be causes of ovarian cancer before your work in this litigation; is that correct?
A. Correct.
Q. When you reached those causation conclusions, did you do so based upon the body of scientific and medical literature?
A. Yes.
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) Did you reach those conclusions in the context of litigation?
A. No.
Q. Did you reach those causation conclusions

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after talking with plaintiffs' counsel?
MS. O'DELL: Object to the form.
A. No.
Q. (BY MR. JAMES) Did you reach those causation conclusions after being provided materials selected for your review by counsel?
MS. O'DELL: Object to the form.
A. (Examined realtime screen.) No.
Q. (BY MR. JAMES) Did you reach those causation conclusions by reviewing unpublished litigation reports?
MS. O'DELL: Object to the form.
A. No.
Q. (BY MR. JAMES) Did you reach those causation conclusions by reviewing company documents?
MS. O'DELL: Object to the form.
A. No.
Q. (BY MR. JAMES) What conclusions did you have, if any, before your work in this litigation on the talc ovarian cancer hypothesis?
MS. O'DELL: Object to the form.
Would you -- would you -- could you just -- I was just reading your question, Scott.

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Is that right?
MR. JAMES: What conclusions.
MS. O'DELL: Okay. Sorry.
A. I was concerned about talc products being transported through the female genital tract because of findings in the '70s of talc deeply embedded in ovarian tissue.
J. Don Woodruff was one of my mentors, and he shared this information with me in 1979; and I found it concerning. He went on or was in the position at that time of postulating talc -- talcum powder as an etiologic factor in the development of ovarian cancer. This is well before the publication of the epidemiologic studies, and I registered his concerns in my brain.
Q. (BY MR. JAMES) And with that statement, then, are you indicating that those concerns -- you did not express those concerns to anyone else, correct?
MS. O'DELL: Object to the form. Misstates her testimony, but go ahead.
MR. JAMES: I don't want to do that, so let me start over.
A. Okay.

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Q. (BY MR. JAMES) When you said you registered those concerns in your brain, what do you mean by that?
A. I never used talcum powder products on my female children, and I don't have any male children, so that's pretty much -- and I didn't use talcum powder products on myself, and I felt strongly about that.
Q. And what time frame was that?
A. Well, I heard from him in 1979 in my first trial, and I didn't use talcum powder from 1979 to 1992 when my first daughter was born, nor did I use it in 1994 for diapering my second daughter; and we just didn't have powder in my home.
Q. Did you express those concerns in writing anywhere?
A. No.
Q. We discussed this already this morning, but did you express those concerns to any of the patients that you treated?
A. No.
Q. Same line of questions but with respect to asbestos. Okay?
Did you conclude before -- what --

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what conclusions had you come to, if any, before your work in this litigation about a relationship between asbestos and ovarian cancer?
A. Prior to my work in this litigation, I did not have an awareness of the relationship of asbestos to ovarian cancer.
Q. Is that an opinion, then, that you've formed in the context of litigation?
MS. O'DELL: Object to the form.
A. After my review of the scientific data, yes.
Q. (BY MR. JAMES) And to be clear and to respond to the objection, the question I'm asking is: Did you reach the opinion about the relationship between asbestos and ovarian cancer in the context of this litigation?
A. I think it's unfair to say "context of litigation." I would have -- had I reviewed all that literature, I would have reached that conclusion whether or not this litigation was ongoing or not.
Q. If you don't like the word "context," I can rephrase.
Did you reach the asbestos conclusions

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that you've rendered in your report after being retained in this litigation?
A. Yes, correct.
Q. On that note, Dr. Smith, let's look at page 21 of your report, please.
A. (Complied.) Excuse me.
Q. And you see at the bottom of page 21, Dr. Smith, you have a section that's labeled "Summary of my opinions."
Do you see where I am?
A. Yes, sir.
Q. And Item Number 1 is the opinion that you hold today that talc causes ovarian cancer, correct?
A. Correct.
Q. And we've discussed this already, but that is an opinion that you've formed after being retained in the litigation, correct?
A. Correct.
Q. With respect to Item Number 2, you have opined that "There is credible evidence that Johnson and Johnson baby powder products contain asbestos."
Do you see where I read?
A. I do.

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Q. Is that an opinion that you formed after your retention in this litigation?
A. Correct.
Q. Then you have the opinion that asbestos and fibrous talc cause ovarian cancer.
Again, those are opinions that you've formed after being retained in the litigation, correct?
A. Correct.
Q. And then continuing on to Number 2, the opinion that you've formed concerning heavy metals, is that an opinion that you formed after being retained in the litigation?
A. Correct.
Q. With respect to -- and the same is true with fragrances, is that an opinion that you formed after being retained in the litigation?
A. Correct.
Q. And Item Number 3, you express opinions concerning inflammation.
Is that a fair paraphrasing of Number 3?
MS. O'DELL: Objection to form.
A. I don't think those are opinions. I think

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those are facts. Those are scientific facts. They've been demonstrated in the laboratory.
Q. (BY MR. JAMES) You understand that you have been retained to offer your scientific opinions in this litigation, right?
A. Yes. Yes.
Q. And so Number 3, do you hold the opinion that you've expressed in Number 3?
A. Yes.
Q. Is that an opinion that you've formed after being retained in the litigation?
A. Yes.
Q. And Number 4, do you see where I am still?
A. I do.
Q. Okay. And Number 4 is an opinion concerning migration and also an opinion concerning inhalation, correct?
A. Yes.
Q. Are those opinions that you've formed after being retained in this litigation?
A. Correct.
Q. Turning to the opinion that you have expressed that there is, quote, "credible evidence," close quote, that Johnson's Baby Powder products

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contain asbestos, what is the credible evidence that you rely upon?
A. The paper of Blount in 1991 and the report of Dr. Longo and the other doctor with him whose name I forgot. It starts with an R, I think.
MS. O'DELL: I think you mean Rigler.
THE WITNESS: That's it. Starts with an R.
Q. (BY MR. JAMES) Are those the litigation reports in litigation testimony that we previously discussed?
A. Yes, sir.
Q. Is there any other evidence that you consider -- that you have considered that supports your opinion that there's, quote, "credible evidence" of asbestos in those products?
MS. O'DELL: Object to the form.
A. I can't remember any other evidence or references.
Q. (BY MR. JAMES) You cite some articles on page 18 of your report?
A. Oh, yes.
Q. Do you see where I am, Doctor?
A. Yes.

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Q. And you cite a number of articles there.
Do you see where I'm looking in the first paragraph?
A. (Examined exhibit.) Yes.
Q. Okay. In that -- the first paragraph in that section?
A. Yes.
MS. O'DELL: And we're -- just for purposes, we're at page 18?
MR. JAMES: Correct.
THE WITNESS: Yeah. We're talking about the first sentence.
MS. O'DELL: Okay.
Q. (BY MR. JAMES) How did you obtain those articles?
A. Those articles were provided for me as reference materials by the plaintiffs' attorneys.
Q. Do any of those articles pertain to Johnson & Johnson products?
A. Blount disclosed in her deposition that it was Johnson & Johnson Baby Powder.
Q. And I'm -- just to be clear, I'm asking about the articles that you've cited in the first paragraph in the asbestos section on page 18.

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A. Blount's one of those articles -- well, her article -- the deposition is not the paper. You're right. Sorry.
Q. No, that's fine.
A. I don't know that any of those were Johnson & Johnson Baby Powder.
MS. O'DELL: Just to be -- if you're referring to -- when you say "those," it's not clear on the record, so if there's something specific -- you don't have to go back, but just be -- be cognizant of that.
Q. (BY MR. JAMES) What level of review did you undertake to collect literature on the topic of the alleged presence of asbestos in talcum powder products?
MS. O'DELL: Object to the form.
A. (Examined exhibit.)
MS. O'DELL: If you understand the question.
THE WITNESS: I understand the question.
A. I mean, I remember Googling that question and getting into a lot of craziness on the internet that I didn't want to be in. I relied on the

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reports provided to review.
Q. (BY MR. JAMES) And those were the reports provided to you by plaintiffs' counsel?
A. Yes.
Q. And you also cited a number of articles that you just testified were provided to you by plaintiffs' counsel?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) Did you find any articles through your searches that contradicted the information provided to you by plaintiffs' counsel?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) Where are those articles cited in your report?
A. I don't think I have cited them in my report.
Q. You found articles that contradict the allegation that asbestos is a contaminant in talcum powder products, correct?
MS. O'DELL: Object to the form.
A. It's not a contradiction. The absence of something does not contradict the presence of

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something.
Do you understand?
Like in Longo's report, he found asbestos in 63 percent of his samples. He did not find asbestos in 34 percent of his samples. The fact that he didn't find it in 34 percent does not mean he didn't find it in 66.
Asbestos is a carcinogen and its significance in risk to life is when you find it.
In the FDA report that did not find asbestos in Johnson's Baby Powder, Shower to Shower, and in multiple samples from suppliers of ore -- I mean, that's great that they didn't find it, but it doesn't mean it's not detectable. And I can't explain in terms of being an expert in technique to understand why some people found it and some people didn't find it.
Does that make sense to you?
Q. (BY MR. JAMES) I think you answered a question that I didn't ask, so let me rephrase.
A. I'm sorry.
Q. In searching for literature about the alleged presence of asbestos in cosmetic talc, did you find any articles -- published articles that

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reach the conclusion that there was no such contamination?
MS. O'DELL: Object to the form.
A. I can't remember any.
Q. (BY MR. JAMES) If you had found those, would you have discussed those in your report?
A. Probably. I mean, I want to be comprehensive.
Q. And so if there is a body of literature out there that you didn't discuss in your report, then you would agree that your analysis of the issue was not comprehensive, correct?
MS. O'DELL: Excuse me. Object to the form; misstates her testimony.
A. If I missed it, I shouldn't have.
Q. (BY MR. JAMES) And, Dr. Smith, you did just mention the FDA testing of talc for the presence of asbestos, correct?
A. Yes.
Q. And have you reviewed that testing?
A. I've reviewed that report.
Q. The FDA's report?
A. Yes.
Q. Did you discuss it at all in your

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litigation report?
A. No.
Q. And why is that?
A. I explained that. Negative isn't as significant as positive.
Q. Is that because the positive testing results supports your litigation opinion; the negative testing results do not?
MS. O'DELL: Object to the form.
A. No. It's because the positive testing is a threat to human life.
Q. (BY MR. JAMES) So you have seen -- I'm gonna mark as Exhibit Number 7 the 2007 -- excuse me, the 2010 FDA testing on cosmetic talc.
A. Yes.
(Deposition Exhibit 7 marked for identification.)
Q. (BY MR. JAMES) Is that a printout of the testing information you have reviewed, Dr. Smith?
A. That is identical to what I have reviewed.
Q. Okay. Do you have any reason to disagree with the FDA's findings here in this Exhibit 7?
MS. O'DELL: Object to the form to the degree -- what findings are you referring to in your

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question?
MR. JAMES: The findings in Exhibit Number 7.
MS. O'DELL: Object to the form.
A. Their -- I -- they said, "No asbestos detected."
I can -- I don't know enough about testing to disagree with them, but I don't know what -- I mean, does "none" mean zero or does "none" mean below some level?
I do know that their technique -- I know enough to know that it's a good means of finding asbestos by, you know, polarized light microscopy followed by TEM, that that's a good technique.
I don't understand why theirs are so different from the other, and I don't have the expertise to go any further than that.
Q. (BY MR. JAMES) With respect to whether there is asbestos in the cosmetic talc products or there isn't, is it fair to say that you would defer to others?
A. Yes.
MS. O'DELL: Object to the form.

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Q. (BY MR. JAMES) And do you consider yourself to be an expert in mineral classification?
A. Absolutely not.
Q. What about an expert in mineralogy?
A. Absolutely not.
Q. But you understand the FDA's testing was performed by an independent lab?
A. Yes, they said that.
Q. And that's contrasted, which you understand that Longo's testing is done by a paid litigation expert, correct?
MS. O'DELL: Object to the form.
A. I'm kind of thinking they probably paid the lab they sent it to too. I mean, shouldn't they?
Q. (BY MR. JAMES) And who's -- who is "they"?
A. The FDA paid the AMA Analytical Services.
Q. Okay. Do you have any understanding of how the lab results by the FDA were obtained or paid for?
A. No.
Q. Do you have an understanding of -- did you know that the FDA's testing was performed outside

the context of litigation?
MS. O'DELL: Object to the form.
A. I hadn't thought of it, but I would not think it's about litigation.
Q. (BY MR. JAMES) And if we looked at the front page of Exhibit Number 7, which I've handed you, have you reviewed the text of this exhibit before today?
A. This whole -- yes.
Q. Okay.
MS. O'DELL: And if you need to look --
Q. (BY MR. JAMES) And do you understand that this exhibit --
MS. O'DELL: Excuse me. Excuse me.
If you -- and if you need to refresh yourself on any part of the text, Doctor, feel free to do that as he's asking you questions.
THE WITNESS: Okay.
MR. JAMES: Absolutely. Certainly.
Q. (BY MR. JAMES) If you turn to the second page of the exhibit, do you see the section that's titled "How FDA followed up on the latest reports"?
A. Yes.

Q. Okay. And you see it says, quote, "Because safety questions about the possible presence of asbestos in talc are raised periodically, the FDA decided to conduct an exploratory survey of currently marketed cosmetic-grade raw material talc," closed quote.
Do you see where I read?
A. Yes.
Q. And there's no discussion there that the testing was done at the behest of litigation, is there?
A. No.
Q. And did you know that the talcum products tested by the FDA in this document were Johnson & Johnson products?
MS. O'DELL: Object to the form.
A. I think it says Johnson's Baby Powder and Shower to Shower on there, and I know those are J&J products.
Q. (BY MR. JAMES) Do you have any personal knowledge concerning the specifications that are used by Johnson & Johnson with respect to its cosmetic talcum powder products?
A. I do not know them.

Q. Have you looked at those?
A. No, I have not.
Q. Are you aware that Johnson & Johnson manufacturers its products in accordance with United States Pharmacopeia Convention?
MS. O'DELL: Objection to form.
A. I did not know that specifically.
Q. (BY MR. JAMES) Have heard of that organization before?
A. Yes, I have.
Q. Do you consider that to be a respected organization?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) Did you know that there have been thousands upon thousands of testing documents produced in this litigation?
MS. O'DELL: Object to the form.
A. I --
MS. O'DELL: Don't speculate. If you -- if you --
THE WITNESS: I --
MR. JAMES: I'm asking her if she knew.

THE WITNESS: -- was going to say I didn't know.
MS. O'DELL: Okay. Good. I didn't hear what your answer was. Sorry.
THE WITNESS: Okay.
MS. O'DELL: I didn't -- I talked over you. I apologize.
THE WITNESS: That's okay.
Q. (BY MR. JAMES) So the -- just so that the exchange is clear, Doctor, did you know that there have been thousands upon thousands of testing documents produced in this litigation?
A. I did not.
Q. Did you know that those testing documents include testing documents performed by third-party labs?
MS. O'DELL: Object to the form.
A. I did not.
Q. (BY MR. JAMES) Did you review a 2014 letter by the FDA in the course of forming your opinions in this case?
A. Could you show me that letter?
Q. Absolutely.
A. See if I recognize it.

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MR. JAMES: I'm gonna mark as Exhibit Number 8 -- it's the 2014 FDA letter denying the Citizen Petitions.
(Deposition Exhibit 8 marked for identification.)
A. (Examined exhibit.) Yes, sir, I have seen this letter.
Q. (BY MR. JAMES) Did you consider this letter informative -- to be informative of your opinions?
MS. O'DELL: Object to the form.
A. I read this report, and it went into a total database.
Q. (BY MR. JAMES) And does that mean your total set of materials that you considered?
A. Yes, it's my brain.
Q. Do you understand that in this letter the FDA also commented on the allegation that asbestos contaminates cosmetic talc products?
A. Yes.
Q. And did you -- do you recall seeing the FDA's conclusion in this letter about that allegation?
MS. O'DELL: Feel free to refresh

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yourself about the document, Dr. Smith.
A. (Examined exhibit.) My understanding was their conclusions was that they were not going to issue a warning on products, nor were they going to allow a hearing for further discussion.
Q. (BY MR. JAMES) And you understand that in this 2014 letter the FDA referred back to its 2010 testing for presence of asbestos, correct?
A. Correct.
Q. Do you have any reason to disagree with the FDA's statements in this letter about the allegation that asbestos contaminates talc products?
MS. O'DELL: Objection to the form.
I think Dr. Smith misunderstood your prior question. Counsel, I think you sort of missed each other.
But your context of this question is asbestos, not the overall finding of the letter, but asbestos itself?
Q. (BY MR. JAMES) Dr. Smith, can you answer my question?
A. I may have to read it again.
(Examined realtime screen.) Yes, they did refer back to the 2010 testing for presence of

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asbestos.
Q. (BY MR. JAMES) And my -- the question that I posed before Ms. O'Dell made her speaking objection was that do you have any reason to disagree with the FDA's statements in this letter about the allegation that asbestos contaminates talc products?
MS. O'DELL: Object to the form; misstates the document.
A. (Examined realtime screen.)
I share the FDA's concern that they make a blanket statement with testing only some of the suppliers and a limited number of products and a limited number of samples of those products, so I -- I understand they -- how they base their conclusion. I might have or would have suggested additional studies.
Q. (BY MR. JAMES) And you understand -- again, we've discussed this already, but of the products tested, those products included Johnson & Johnson products.
Did you know that?
A. Yes. I -- they had a single sample of Johnson & Johnson powder from the DC area.

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Q. Do you understand that the supplier of the talc that's used in Johnson & Johnson products also submitted samples?
A. Yes, I did.
Q. Do you have any opinions about the amount of exposure to asbestos that you believe would be imparted upon a user of Johnson & Johnson talc products?
MS. O'DELL: Object to the form; vague as to time and duration.
A. No.
Q. (BY MR. JAMES) And do you have any opinions about the alleged contamination on a fiber-per-bottle basis?
MS. O'DELL: Object to the form.
A. No.
Q. (BY MR. JAMES) Do you have an opinion as to when you believe J&J talc powder products were contaminated with asbestos and on the market?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) What is that opinion?
A. My opinion is that contamination occurs at the mine and persists through the processing all the

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way to market.
Q. Okay. I think you misunderstood my question or maybe I asked a bad question.
But do you have any opinion about when, for what duration or period of years, Johnson & Johnson talc products were on the market and were allegedly contaminated with asbestos?
MS. O'DELL: Object to the form.
A. Dr. Longo has tested samples from the '70s to 2000 with the presence of a -- presence of asbestos.
Q. (BY MR JAMES) And, again, you're referring back to the Longo litigation testing that we've talked about at length --
A. Yes.
Q. -- this morning, correct?
A. Yes.
MS. O'DELL: Objection to form. Excuse me. Object to the form.
Q. (BY MR. JAMES) Do you have any opinion about -- well, strike that.
With respect to your opinion that asbestos is a cause of ovarian cancer, how did you go about searching for the materials that you

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reviewed to inform that opinion?
A. I reviewed articles that were listed in IARC 100C and --
Q. And the -- oh, I'm sorry, Doctor.
A. -- then PubMed research as well.
THE COURT REPORTER: What did you say?
THE WITNESS: PubMed, P-u-b-M-e-d
Q. And on page 18 through 19, Doctor, is, again, your section on asbestos, correct?
A. Um-hum. Um-hum.
Q. And in that section, Doctor, you refer to the IARC, which you just mentioned, correct?
A. Correct.
Q. And then you cite five, what you refer to as, quote, "heavy occupational exposure," close quote, studies, correct?
A. Correct.
Q. And below that you also discuss the Camargo study; is that right?
A. Correct.
Q. And then if you turn the page, you refer in a single sentence to a Reid study, correct?
A. Correct.
Q. Did you review all of those studies?

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A. Yes.
Q. Okay. Did you review any other studies examining the purported relationship between asbestos and ovarian cancer?
A. Not that I remember.
Q. Does this report reflect your complete analysis of those studies?
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) And how they relate to your opinions in this case?
MS. O'DELL: Objection to form.
A. Yes. I believe so.
Q. (BY MR. JAMES) Do you recall looking at the Reid study? Do you -- sitting here today, do you recall the Reid study?
A. That's my favorite one. May I see it.
Q. Sure.
MS. O'DELL: Yes. Please.
Q. (BY MR. JAMES) Did you say -- I'm sorry.
Did you say the Reid study was your favorite study?
A. Yes.
MS. O'DELL: On this topic, Doctor.
THE WITNESS: In my life, no. It is

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not my favorite study in my life, but . . .
MR. JAMES: Okay. I'm gonna mark the Reid study as Exhibit Number 9.
(Deposition Exhibit 9 marked for identification.)
A. (Examined exhibit.)
MR. JAMES: Oh, thank you.
Q. (BY MR. JAMES) Have you had a chance to refresh your recollection of the study, Doctor?
A. Um-hum. Um-hum.
Q. And why is this your favorite study?
A. As a pathology review discriminating mesothelioma from epithelial ovarian cancer.
Q. And you don't have any -- strike that.
The discussion that you've included in your report as to Reid is that single sentence, correct?
A. Yes.
Q. Do you --
A. And it's a meta-analysis.
Q. Do you agree with the statements in the Reid study about misclassification?
A. Exactly what statements, please?
Q. Sure.

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So if you look towards the Conclusion section that's on the second to last page of the article.
A. (Complied.) Thank you.
Q. And if you look at the Conclusion section, I'll just read the first couple sentences.
The article says, quote, "Taken without further analysis, women thought to have ovarian cancer had an increased rate in the meta-analysis if reporting having been exposed to asbestos, compared with reference populations." (Paraphrasing.) However, this finding may result from the methods used to identify the ovarian cancer cases, close quote.
A. Yes.
Q. Do you agree with the concern expressed in Reid about the disease misclassification?
A. I do.
Q. And then if you scan further down in that paragraph of the article, Doctor, you see, you know, about halfway to three-quarters of the way down, there's a sentence that starts with the word "However."
It says, quote, "However, the authors

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of this article suggest that the IARC decision to determine asbestos exposure as a cause of ovarian cancer was premature and not wholly supported by the evidence" --
A. Are you on the back page?
Q. -- close quote.
Yes. On the same paragraph that I was reading with you earlier. It's the Conclusion paragraph.
A. Where it says "Discussions"? Oh, no.
Q. I'm on page --
A. Oh, I'm --
Q. -- 1294.
A. Okay. I've caught up with you now. Sorry. (Examined exhibit.)
Q. And I was reading a sent- -- a sentence that started with the word "However."
A. All right. Um-hum. (Examined exhibit.)
Q. Do you agree with the Reid authors that the determination of IARC was premature?
A. No, I do not.
Q. Do you agree with the authors of the Reid paper that the IARC conclusion was not wholly supported by the evidence?

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A. I think the weight of the evidence falls with the IARC even though they're meta-analysis crossed -- their -- no, their meta-analysis didn't.
The overall -- I mean, their findings have a risk of 1.75 with confidence intervals of 1.45 to 2.10.
So, again, she has a positive study with pathology review, and then she says the IARC is premature. I don't understand her conclusion.
Q. Do you understand that, again, her -- her -- the cautions expressed in this last paragraph, some of those cautions arise from the concerns about disease in this classification.
Do you understand that?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) And do you agree with those concerns?
MS. O'DELL: Object to the form.
A. I think it is very difficult to discriminate mesothelioma from epithelial ovarian cancer sometimes.
Q. (BY MR. JAMES) And I received word that the tape needs to be changed so --

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A. Okay.
Q. -- we'll take a short break.
A. Okay.
THE VIDEOGRAPHER: Going off the record. The time is 11:39 a.m.
(A recess was taken from 11:39 a m. to 11:55 a m.)
THE VIDEOGRAPHER: This marks the beginning of Disk 2. Back on the record. The time is 11:55 a m.
Q. (BY MR. JAMES) Dr. Smith, we are continuing our discussion of your opinion on asbestos as causes of ovarian cancer. Okay?
A. Correct.
Q. Did you consider any weaknesses or limitations in the body of the literature that you reviewed concerning the link between asbestos and ovarian cancer?
A. Could you be more specific?
Q. Certainly in evaluating medical literature you would agree that one thing for you to consider is whether the study has any limitations, correct?
A. Correct.
Q. And so my question, which is open-ended,

is whether, in looking at the set of literature that you looked at on asbestos and ovarian cancer, if you found any limitations to that set of literature?
MS. O'DELL: Objection; vague.
A. I've considered whether they're single site studies, occupational spsoure -- exposure versus people who wash the clothes of workers or nonenvironmental exposure as opposed to occupational, those things.
Q. (BY MR. JAMES) And --
A. And --
Q. -- so let's start --
MS. O'DELL: I'm sorry. Were you finished, Dr. Smith? If you --
THE WITNESS: I have.
MS. O'DELL: Okay.
Q. (BY MR. JAMES) Let's -- so you just identified one limitation as -- let me -- let me rephrase this.
Would you agree that one limitation of the set of literature that you reviewed was that --
(Phone interruption.)
THE WITNESS: What is that?
MR. JAMES: Just a second. Let's go

off.
THE VIDEOGRAPHER: Going off the record. The time is 11:57.
(A recess was taken from 11:57 a m. to 11:58 a m.)
THE VIDEOGRAPHER: Back on the record. The time is 11:58 a m.
Q. (BY MR. JAMES) Dr. Smith, would you agree that one limitation to this set of literature that you reviewed is that the literature pertains to occupational exposures?
MS. O'DELL: Object to the form.
A. It contains occupational exposure and, I mean, the meta-analysis of Reid, for example. It contains both.
Q. (BY MR. JAMES) Do you -- would you agree that for the studies that pertain to occupational exposure that you've reviewed that's one limitation to those studies in applying them to the --
A. Nonoccupational people, yes.
Q. Thank you. And the doctor finished my question.
A. Sorry.
Q. And I -- we understood each other, so

that's okay. I'll try to talk quicker, and you can try to anticipate my questions less.
MS. O'DELL: Well, and if you would -- yes, and give me a moment just to respond --
THE WITNESS: Sorry.
MS. O'DELL: -- respond with an objection if I need to.
THE WITNESS: I'll get better.
MS. O'DELL: Thank you. You're doing great.
Q. (BY MR. JAMES) You agree that long-term exposure to asbestos in an indust- -- in an industrial environment is different than the allegation that a person's exposed to asbestos-contaminated talc products --
MS. O'DELL: Object --
Q. (BY MR. JAMES) -- correct?
MS. O'DELL: Object to the form.
A. If you are talking about difference in terms of dosage and -- and amount of exposure, then I would say there's probably a difference.
If you would suggest that the mechanism of carcinogenesis is different, then I would say no, it's probably the same.

Q. (BY MR. JAMES) And you agree that some of the studies that the IARC looked at were in the occupational context, correct?
A. Correct.
Q. And, in fact, the IARC's conclusion on causation was heavily weighted on the occupational studies, correct?
MS. O'DELL: Object to the form.
A. I'd have to look at the IARC study again to see how they stated it. And I could do that, if you want me to.
Q. (BY MR. JAMES) Do you recall that when the IARC looked at the nonoccupational studies the association that they found there was not statistically significant?
MS. O'DELL: Objection to the form.
A. I don't recall that.
Q. (BY MR. JAMES) If that's the case, do you believe that's important?
MS. O'DELL: Object to the form.
A. I'd like to look at the paper if you'd let -- if you'd let me.
Q. (BY MR. JAMES) Sure.
THE WITNESS: Am I allowed to see it?

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Q. (BY MR. JAMES) That's fine. That's fine.
Let's talk about -- talk about --
we'll talk about the paper more -- more specifically in just a second.
A. Okay.
Q. If I can continue the line of questions on the limitations.
A. Okay.
Q. So we've talked about occupational --
MS. O'DELL: Excuse me.
Q. (BY MR. JAMES) -- being one limitation, correct?
MS. O'DELL: Excuse me. Doctor --
MR. JAMES: Leigh, there's not a question pending.
MS. O'DELL: She's asked to look at IARC 100C, and if the witness has asked to look at the document, I'm going to put it in front of her. Give me just a second.
THE WITNESS: It's the second IA. It's the first thing in the second IA.
MS. O'DELL: (Handed binder to witness.)
THE WITNESS: Thank you.

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A. (Examined binder.)
Q. (BY MR. JAMES) Okay. Dr. Smith, your counsel has handed you a copy of the IARC talc monograph, correct?
A. Correct.
Q. Okay. And I'm gonna mark as Exhibit Number 10 --
MS. O'DELL: I'm sorry. You said the talc monograph. I handed her 100C. Not --
MR. JAMES: Oh. Thank you.
BY MS. O'DELL: Not monograph.
MR. JAMES: You're right.
BY MS. O'DELL: 193.
MR. JAMES: You're right. You're right. Thank you.
Q. (BY MR. JAMES) So I am going to -- I'll refer to it commonly as the asbestos monograph for -- for a simple shorthand.
So your counsel has handed you a copy of the asbestos monograph 100C and --
MS. O'DELL: Which -- which discusses talc, so I don't want to be misleading.
THE WITNESS: No, 193 discusses talc. 100C discusses asbestos.

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Q. (BY MR. JAMES) So I'm going to hand you -- I think we're all on the same page now. I'm gonna hand you also a copy with some excerpts from 100C. Okay?
A. Okay.
Q. And I'm gonna mark it as Exhibit Number 10.
(Deposition Exhibit 10 marked for identification.)
MS. O'DELL: Thank you. Feel free to refer to the whole monograph if you'd like, Doctor -- Dr. Smith.
THE WITNESS: Okay.
A. I turned right to it.
Q. (BY MR. JAMES) Okay. Doctor, if you can look at page 256 --
A. Yeah.
Q. -- of either the exhibit that I handed you with the excerpts or you're welcome to look at the larger monograph as well.
A. I'm there.
Q. And if you look at the right-hand column, it's the first full paragraph in that column. It starts with "The Working Group."

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Do you see where I'm reading?
A. Um-hum. Um-hum. Yes.
Q. And if you look down at the bottom half of that paragraph, the IARC Monograph states, quote, "The conclusion received additional support from studies showing that women and girls with environmental, but not occupational exposure to asbestos had positive, though non-significant, increases in both ovarian cancer incidence and mortality," close quote.
Do you see where I read that?
A. Yes.
Q. And did I read that correctly?
A. Yes.
Q. So here the IARC is commenting that in the nonoccupational studies the association is not statistically significant, correct?
MS. O'DELL: Object to the form.
A. In the articles, they cited, IARC -- this started in 2009 and was published in 2012, and I do not believe they had the 2011 meta-analysis by Reid in this. They cite Reid 2008 and 2009, but not the meta-analysis. So what they have, they're making their conclusions there.

Q. (BY MR. JAMES) Right.
A. I think this adds to it.
Q. The Reid paper?
A. The 2011 Reid paper.
Q. And the 2011 Reid paper, again, is the paper where the authors conclude that the IARC's finding with respect to asbestos and ovarian cancer is -- may be premature, correct?
A. I disa- --
MS. O'DELL: Object to the form.
A. Yes. You are correct that that is their conclusion. I disagree with their conclusion. It is your Exhibit 9.
Q. (BY MR. JAMES) And so you disagree with the conclusions of -- of the paper that you qual- -- that you categorized as one of your favorites, correct?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) And if you look up on the same paragraph, Dr. Smith --
A. Um-hum.
Q. -- the first sentence of that paragraph reads, quote: (Paraphrasing.) The Working Group

noted that a causal association between exposure to asbestos and cancer of the ovary was clearly established, based on five strongly positive mort- -- mortality studies of women with heavy occupational exposure to asbestos, close quote.
Do you see that?
A. Correct.
Q. So, again, the IARC here is emphasizing that the body of literature that supports the IARC's finding is the occupational body of literature, correct?
MS. O'DELL: Objection to the form.
A. Correct.
Q. (BY MR. JAMES) Are there any other limitations that -- that you can think of with respect to this set of literature?
And when I say "set," I refer to the literature exploring the relationship between asbestos and ovarian cancer.
A. In IARC --
MS. O'DELL: Object to the form; vague.
A. -- 100C.
Q. (BY MR. JAMES) The -- yes. My question

posed is about the body of literature that you reviewed to inform your opinions about asbestos and ovarian cancer.
Are there any other limitations that you can identify for us today?
MS. O'DELL: Objection to form; vague.
A. I think the IARC -- I forgot how to speak English. Sorry.
The IARC conclusion that asbestos is causative in ovarian cancer is expanded by two meta-analyses as opposed to these single studies, EPI studies, even though they're cohort studies of Camargo and Reid.
Reid doesn't agree with her own statistical findings. I don't know why she did that.
Q. (BY MR. JAMES) Well, the Reid authors considered the limitations of the body of literature, correct?
MS. O'DELL: Object to the form.
A. Everyone considers the limitations of the body of literature when they write a paper.
Q. (BY MR. JAMES) Right. So do you -- do you think Reid did anything incorrectly in

evaluating the limitations of the body of literature?
A. I think she made an incorrect conclusion. I don't think that necessarily has to do with the limitations of the body.
She has statistically significant meta-analytic study even though the strength is low, but she -- and then she says -- I disagree with it. I don't think it's significant.
I mean, it's 1.75. What -- I don't -- I don't understand how she reached her conclusion.
Q. But you understand she -- the paper notes the concern for misclassification, which we've already discussed, correct?
A. Right. But she accounted for that in her studies, so I --
Q. What do you mean by that?
A. She had a patholo- -- she had pathologic review accounted for within here too.
MS. O'DELL: When you say "here," you're referring to Exhibit 9, the Reid paper?
THE WITNESS: Yes.
MS. O'DELL: Okay.
THE WITNESS: Sorry. I wasn't clear,

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and the camera probably can't see it too.
Q. (BY MR. JAMES) So the authors of the Reid paper conclude that disease misclassification may be such a problem such that the IARC's conclusion may be premature?
MS. O'DELL: Objection to --
Q. (BY MR. JAMES) And you're saying that the authors --
MS. O'DELL: Excuse me. Have you finished your question? Sorry.
MR. JAMES: No.
MS. O'DELL: Okay.
Q. (BY MR. JAMES) You're saying the author's just got it -- got it wrong?
MS. O'DELL: Object to the form.
A. I disagree with their conclusion.
Q. (BY MR. JAMES) So with mis- -- with this set of literature we've talked about two limitations so far: Misclassification and occupational versus nonoccupational, correct?
A. We've talked about those two things, yes.
Q. Are there any other limitations to the body of literature that you reviewed that you can identify today?

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MS. O'DELL: Object to the form; vague.
A. No.
MS. O'DELL: Are you limiting that to asbestos and ovarian cancer or are you limit -- I mean --
MR. JAMES: Yes. We're talking about the subset of literature, which I've said several times, pertaining to the allegation that asbestos is causative of ovarian cancer. That's what we're talking about right now.
MS. O'DELL: That makes it clear. I don't want something taken out of the record later and it's not -- it's not clear.
MR. JAMES: Fair enough.
A. We've talked about those things. At this time, I can think of nothing else.
Q. (BY MR. JAMES) Do you consider the small number of cases to be a limitation to that body of literature pertaining to the allegation that asbestos is -- is a cause of ovarian cancer?
MS. O'DELL: Object to the form.
A. (Examined exhibit.) I'm looking at the numbers in the Reid study, and I'm sorry, it's

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taking me a minute here, Table 2.
Small number of cases. When they are talking about all cases combining, studying 5,240 cases, is that a small number?
Q. (BY MR. JAMES) Do you believe there's -- one of the limitations to this body of literature is the small number of cases?
A. No. No.
Q. Do you believe that there are any limitations to this literature associated with the type of asbestos involved in these studies?
A. No.
Q. Are you familiar with the type of asbestos involved in these occupational studies?
A. Each of the studies list types, at least some of them do.
Q. Does that matter to you at all?
A. Big picture, probably not.
Q. Okay. So does the type of asbestos at issue in the studies looked at by the IARC matter to you at all in your opinion that asbestos contamination in talc is causative of ovarian cancer?
MS. O'DELL: Objection to form.

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A. I don't remember a breakdown by type in the IARC by tremolite or actinolite or -- you know, I don't remember that breakdown.
Q. (BY MR. JAMES) And it's not addressed in your report, correct?
A. It is not addressed in my report.
Q. To reach your opinion that asbestos is a cause of ovarian cancer, what methodology did you apply?
A. The same methodology I applied -- I apply every time. I read all the literature that I could find. I read it critically. Went through the tables, read the footnotes, and made a conclusion, as did IARC 100C.
Q. Is your causation opinion based on IARC?
A. I think we reached the same conclusion. I certainly got a bunch of references from IARC.
But as I told you, I make my own conclusions, even when they disagree with an author of a paper. So I'm certainly influenced by their conclusion, but I made my conclusion, and I felt freedom to disagree if I did.
Q. Did you read all the studies that IARC discussed?

A. Yes.
Q. Did you read the nonoccupational studies?
A. I read all of these studies. They are -- I would have to look at them individually or go to details of them.
Q. Is there a reason why you didn't discuss the nonoccupational studies but you did discuss the occupational studies?
MS. O'DELL: Object to the form.
A. I discussed two meta-analyses that include occupational and nonoccupational exposure because, as I stated other places in my report, I give strength to a meta-analysis above a single either occupational or nonoccupational exposure.
Q. (BY MR. JAMES) And in that section, you did cite to the five occupational studies, but you actually don't cite to the nonoccupational studies in the text of your report.
And so that's the genesis of my question is: Did you actually look at the nonoccupational studies?
MS. O'DELL: Objection to form; asked and answered.
A. If -- if there's a study that's -- that I

didn't cite, I -- I don't believe I -- I don't remember it.
Q. (BY MR. JAMES) Later on in your analysis with respect to talc and ovarian cancer you talk about the importance of strength, correct?
A. Part of the Bradford Hill criteria, yes.
Q. And did you consider strength with respect to asbestos and ovarian cancer?
A. I thought it was interesting that the strength of the relative risk or overall risk was similar between talc and asbestos.
For Reid, it was 1.75.
For Camargo, it was pretty close to that. I don't remember the exact number. I don't think -- I mean, do you want to know the exact number? Wait, wait. I may have said it in my report.
(Examined exhibit.) Yeah, 1.77. Yeah, that's almost exactly the same thing and almost exactly the same confidence intervals, 1.45, 2.1, 1.37, 2.28. So they're, you know, so those two meta-analyses. Now I forgot -- oh, yes. Strength.
I thought -- I thought it was interesting, yes.

Q. Is the odds ratio that you just cited, the odds ratio, applicable to the occupational studies or the nonoccupational studies?
A. Well, there's an occupational one. There's a little bit lower. There tend to be in the -- the statistically significant ones tend to be a 2.27s, 2.53s, not like -- not like asbestos and mesothelioma where the relative risk is 70, you know. I mean, we're talking about a much lower thing.
Q. And, again, we've talked already about the fact of the IARC noted in its analysis that the nonoccupational studies provide a not statistically significant association.
A. Yes.
MS. O'DELL: Excuse me.
Q. (BY MR. JAMES) Correct?
MS. O'DELL: Objection to form.
You may answer.
A. I agree with you, but that's why we have meta-analyses.
Q. (BY MR. JAMES) Do you consider a limitation to the body of literature looking at asbestos and ovarian cancer to include confounding?

A. Tell me what you mean by "confounding."
Q. What does "confounding" mean to you?
A. No, no. You asked -- I asked first.
Q. I know, but I get to ask the questions. That's the way it works.
MS. O'DELL: Object to the form to the extent it's vague and there may be some confusion.
A. For example, I would consider a confounding factor that every one of your asbestos workers are heavy cigarette smokers.
Q. (BY MR. JAMES) And I'll ask a more precise question now.
Did you -- do you recall, in reviewing the body of literature in asbestos and ovarian cancer, that the literature notes an inability to account for confounding factors?
A. Yes. In these studies, they -- they don't -- they have not accounted for factors. Certainly --
Q. And --
A. Yeah.
Q. I'm sorry.
MS. O'DELL: Finish your answer if you'd like to, Dr. Smith.

A. Like genetic. Smoking, genetics, you know, all those things, yes.
Q. (BY MR. JAMES) And you would agree that is a limitation to the set of literature, correct?
A. Yes.
Q. Have you heard of a body of literature referred to as the Miners and Millers studies.
Does that ring a bell to you?
A. It rings a bell.
Q. Do you know if you reviewed those studies in the course of forming your opinions in this case?
A. I'd have to hear an author, but I remember reading about the Miners and Mills [sic] studies.
Q. Did you know that there's a body of literature out there studying cancer rates in miners and millers of cosmetic talc?
MS. O'DELL: Object to the form. It's vague, asked and answered.
A. Without an author, I -- I remember studies by author or perhaps by the first initial of the author's last name, but I don't remember reading something called Miners and Mills studies.
Q. (BY MR. JAMES) If there is a body of literature out there that looks at the cancer rates

of talc miners and millers and that body of literature is not cited in your report, then that means you didn't consider that body of literature, correct?
MS. O'DELL: Objection to form; misstates the record.
A. I don't remember reading that paper. I hope I did.
Q. (BY MR. JAMES) Okay. Can you cite to me -- I'm sorry, Doctor.
A. I would hope I did read the paper, but I didn't. I don't remember it.
Q. Can you point to me anywhere in your report where you would address studies looking at cancer rates in miners and millers of talc?
A. There is not --
MS. O'DELL: Objection to the form.
A. There is not in my report.
Q. (BY MR. JAMES) Within your report, you include some opinions on a phrase that I'll put into quotes, "fibrous talc," close quote.
A. Yes.
Q. You state in your report that "Asbestos and fibrous talc cause epithelial ovarian cancer,"

correct?
A. I do.
Q. Do you equate fibrous talc to be -- to be also talc-containing asbestiform fibers?
A. Fibrous talc is an abest- -- asbestiform habit of talcum powder. So in that -- in that equivalence, they're needlelike particles.
Q. Do you know if the term "fibrous talc" is used in the IARC Monograph?
A. I believe it is.
Q. Do you understand if there is a distinction between fibrous talc and talc-containing asbestiform fibers?
MS. O'DELL: Objection to form.
A. I believe -- wait.
(Examined realtime screen.) I believe there is a distinction. I would really like to find that part because I know it's in here.
(Examined exhibit.) Talcum-containing asbestiform fibers. Talc may also form true mineral fibers that are asbestiform in habit. I used the right word.
"Talc-containing asbestiform fibres is a term that's been used inconsistently in the

literature. In some contexts, it applies to talc containing asbestiform fibres of talc or talc intergrown on a nanoscale with other minerals, including [sic] anthophyllite."
So I think they make distinction between whether it's asbestos or asbestiform habit of talc.
Am I answering your question?
Q. (BY MR. JAMES) I think so.
A. Okay.
Q. Let me ask you this.
A. Okay.
Q. Would you defer to other experts on distinctions or characterat- -- characterizations of fibrous talc versus talc-containing asbestiform fibers?
MS. O'DELL: Objection; form. She just answered your question about that.
A. I believe many mineralogists know more about the forms of talc and minerals than I do. I . . .
Q. (BY MR. JAMES) Have you cited any epidemiologic or medical literature that supports your opinion that fibrous talc is causative of

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ovarian cancer?
A. I have never seen a study that looks specifically with pure fibrous talc and ovarian cancer.
Q. What is the significance of your opinions on asbestos to your opinions on talc and ovarian cancer?
MS. O'DELL: Objection to the form.
A. (Examined realtime screen.) I think the presence of asbestos in talcum powder products causes ovarian cancer.
Q. (BY MR. JAMES) Is the alleged presence of asbestos in cosmetic talc powders critical to your causation opinion that talc powders cause ovarian cancer?
A. No.
MS. O'DELL: Objection to form.
Q. (BY MR. JAMES) Do you believe that talc powders not contaminated with asbestos would also be a cause of ovarian cancer?
A. I'm not sure there is such a thing as a pure, platy talc powder, but I believe such powder use, did it exist, would cause ovarian cancer.
Q. Would your answer hold true if I asked the

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same question about fibrous talc?
MS. O'DELL: Just to be clear --
MR. JAMES: And if you'd like -- I'll just go through it again, which is no problem.
Q. (BY MR. JAMES) Is the alleged presence of fibrous talc critical to your causation opinion that talcum powders cause ovarian cancer?
MS. O'DELL: Object to the word "alleged."
You may answer.
A. I believe that fibr- -- fibrous talc -- a poor preparation of fibrous talc applied repeatedly and consistently to the perineum would cause ovarian cancer.
Q. (BY MR. JAMES) And let me ask a question, maybe, that's more precise, similar to the question I asked you about asbestos.
Do you believe that talc that does not contain fibrous talc is a cause of ovarian cancer?
A. I already answered that.
MS. O'DELL: Object to the form.
A. But I -- but --
Q. (BY MR. JAMES) I think maybe we missed each other.

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A. Okay. You gave me a --
MS. O'DELL: Let him -- excuse me. Let him ask the question and then you respond.
THE WITNESS: Okay.
Q. (BY MR. JAMES) (Examined realtime screen.) So the question that I asked was: Do you believe that talc that does not contain fibrous talc is a cause of ovarian cancer?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) If talc powders did not contain asbestos or fibrous talc, would your opinions about mechanism change?
A. This is kind of a double negative, doesn't it?
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) I don't think it's a double negative.
A. Okay.
(Examined realtime screen.) My opinion about mechanisms unchanged by concerns of asbestos in fibrous talc.
MR. JAMES: It's 12:32. I can continue a little longer if you'd like or -- it's up

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to you Leigh and Dr. Smith.
MS. O'DELL: Dr. Smith, would you like to take a break for lunch now or --
THE WITNESS: Have you got a 10-minute block?
MR. JAMES: I can always go for 10 more minutes.
THE WITNESS: Let's do it.
MR. JAMES: Okay.
THE WITNESS: Is that -- is everybody else comfortable? Yeah, I don't want to --
MS. O'DELL: Yeah. 10 minutes and let's --
THE WITNESS: -- make somebody --
BY MS. O'DELL: -- take a break.
THE WITNESS: -- endure hunger pains.
Q. (BY MR. JAMES) All right. Dr. Smith, we're gonna wade back into your report --
A. Oh, good.
Q. -- and I'm looking at page 3.
And on page 3, Dr. Smith, you list what you consider to be, quote, "generally accepted," close quote, risk factors for ovarian cancer, correct?

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A. I see that.
Q. What is your definition of a generally accepted risk factor?
A. Something that the vast majority of trained physicians in that specialty would accept as truth.
Q. And how did you compile this list?
A. Working in the field for 40 years, viewing lots of risk articles and tabulating them, like listing them and reviewing the literature regarding specific things.
For example, a comprehensive view of the literature regarding tubal sterilization and its risk of ovarian cancer.
Throughout my career, numerous times, I've done ovarian contraceptive use and ovarian cancer of use as formulations of oral contraceptives have changed and different progestins, different levels of estrogen, do we still have a suppressive effect on ovarian cancer? So this is kind of my life.
Q. Do you believe all of the factors that you've listed here in this first paragraph are mentioned in the articles here that you've cited?

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A. I'm not -- without going to each individual article, I can't checklist which thing is listed in each article.
Q. Was it -- when you created this list, was it your intention to cite to an authority that supported each one of these things that you listed at least once?
A. I think -- I don't think everyone -- I can't promise you, without looking at each of these papers, that everybody listed every single one of the things I said, but somebody in this group mentioned these things, and I had other information that maybe want to put on the list.
Q. Is it possible that at least some of these things that you've listed are not identified in the sources that you've cited and instead come from the information that you just referred to that -- that you possessed through your practice?
A. It's possible.
MS. O'DELL: Object to form.
A. It's possible.
Q. (BY MR. JAMES) For -- for example, IUDs that you listed here, do you believe that's a general accepted risk factor for ovarian cancer?

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A. What's -- oh, intrauterine devices. I don't think that's generally -- it's been -- it's been studied in some studies. Pelvic inflammatory disease, it's been plus or minus in some studies.
Q. So --
A. But --
Q. I'm sorry.
A. -- somebody mentioned it somewhere in my -- in my life.
Q. And so the way you've characterized this paragraph is that you have attempted to list, quote, "generally accepted," close quote, risk factors.
And what I'm asking you is whether all these things that you've listed here are, in your opinion, generally accepted by the medical community?
A. I will give you that intrauterine devices may not be generally accepted by the majority of -- I lost my mike. I'm sorry -- obstetrician gynecologists.
Q. And how about PID? Do you believe that's a generally accepted risk factor with the terminology you've used?
A. There -- there are a whole bunch of papers

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about pelvic inflammatory disease and its impact on ovarian cancer and epidemiologic studies and they vary in value.
I would -- it is not as strong a risk factor as inherited gene mutations, family history, nulliparity, and endometriosis.
Q. When creating this list of generally accepted risk factors, did you consult a list of risk factors published by any medical or scientific organization?
MS. O'DELL: Object to the form.
But you . . .
A. I didn't go on any websites to get my references.
Q. (BY MR. JAMES) Would you have consulted the list of risk factors published by ACOG?
A. I didn't get the -- even the committee opinion or the postgraduate, all those different letters, I didn't use that as one of my resources.
Q. And did you consider a list of risk factors published by the SGL?
A. I did not use that as one of my risk factors.
Q. Do you recognize both of those

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organizations as respected scientific organizations?
A. I do.
Q. And you're members of both, correct?
A. I am.
Q. And you have been active in both, correct?
A. Very.
Q. In crafting a list of generally accepted risk factors, why wouldn't you have been interested in what those two organizations have to say about what is, quote, "generally accepted"?
A. I'm not disinterested. I, again, assembled my own sources out of medical databases and read the articles and did my own work.
It's not that I disagree with them. It's just I don't want a copy of their stuff, you know. I want to do my own work.
Q. Earlier you defined "generally accepted" -- and I'll see if I can find it on my realtime.
While I'm looking for it, and you can correct me if I've misstated it, Dr. Smith, but my recall is that you defined "generally accepted" as something that is believed by the majority of practitioners in the field.

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Is that a fair summary?
A. Yes.
Q. Wouldn't it be logical that statements by medic- -- respected medical and scientific organizations with regard to risk factors would be reflective of what the medical community believes --
A. Yes.
Q. -- as a whole?
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) Among that list in the same paragraph, you have listed all of the risk factors.
You also list talc and asbestos, correct?
A. Yes.
Q. And the way you phrase it, I want to be sure that I understand your testimony, but are you testifying here that talcum powder and asbestos are generally accepted risk factors for ovarian cancer?
MS. O'DELL: Object to the form.
A. They are not on the SGO list. They are not -- I mean, on the ACOG list. They are listed in some review articles and the literature about them in risk factors. They are not listed in others.

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I can't give you a percentage, like have a vote in ACOG of who calls it a risk factor and who doesn't. So I don't know what proportion of OB/GYNs believe that's a risk factor or not, but certainly some do, and I can't quantitate it further.
Q. (BY MR. JAMES) And to say something is generally accepted, you'd have to quantify it, wouldn't you?
MS. O'DELL: Object to the form.
A. Yeah. I think generally it would be at 51 percent, and I don't know where the count is.
Q. (BY MR. JAMES) And do you know that the ACOG has actually issued a statement on the talc/ovarian cancer hypothesis?
MS. O'DELL: Object to the form.
A. I have read a very brief statement on the ACOG website about talc.
Q. (BY MR. JAMES) And, again, is -- so because you consider it to be a well-respected organization, you would be interested in what that organization has to say about the hypothesis, correct?
A. That's why I looked it up.

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Q. And do you -- did you -- do you recall, if you've looked at that statement, that they say that there is, quote, "No medical consensus that talcum powder causes ovarian cancer," closed quote?
A. That was the final line, I think, a first line -- first part of what I read was "Don't use it" because of the -- I can't -- I can't quote it out of my brain. But just the "Don't use talc." We haven't got medical consistent is the very short statement I remember reading some time ago.
Q. Okay. I'm gonna mark that, the ACOG statement that I'm discussing --
A. Oh. Well, good.
Q. -- with you, Dr. Smith, as Exhibit Number 11.
A. Don't make me dig so far back.
MS. O'DELL: Exhibit 11?
MR. JAMES: Yes.
BY MS. O'DELL: Thank you.
MR. JAMES: That's where we are.
BY MS. O'DELL: Is this the . . .
MR. JAMES: And I'm sorry for the small print.
(Line intentionally left blank.)

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(Deposition Exhibit 11 marked for identification.)
A. (Examined exhibit.) Okay. "Obstetrician gynecologists do not remend -- recommend use of vaginal treatment such as douche, vaginal sprays or talcum powder and the use of talcum powder has declined over the years. There is no medical consensus that talcum powder causes ovarian cancer."
Q. (BY MR. JAMES) Right. And so we've talked about that last sentence already, correct, where they -- ACOG has published a statement saying there's not a medical consensus, correct?
A. Yes.
Q. Okay. And the first portion of the statement that you've read into the record about the gynecologists not recommending the use --
A. Um-hum.
Q. -- can you read the first part of that sentence for me?
A. "Because of concerns regarding potential discomfort or pain."
Q. And so the recommendation to not use the talcum powder products there is predicated on concern for discomfort or pain, correct?

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MS. O'DELL: Object to the form.
A. That's what it says, but -- so -- and the number of references they cite here are puny compared to a number of studies that I reviewed in-depth. I --
Q. (BY MR. JAMES) Do you believe the ACOG --
MS. O'DELL: Excuse me, sir. Let her finish the --
Q. (BY MR. JAMES) Oh, I'm sorry. I thought you were.
MS. O'DELL: Yeah.
You may finish, Dr. Smith, if you'd like.
A. Reading between the lines and knowing some of the people involved, they don't want to incur criticism for saying, "Because of our concerns about a potential for the development of ovarian cancer, obstetrician gynecologists do not recommend the use of vaginal treatments," so they threw in "potential discomfort or pain."
Now, women frequently use douches, sprays, or powder because they're uncomfortable. It's not because they cause discomfort.
So the people behind the statement

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don't want women to use talcum powder products and aren't willing to call its relation to ovarian cancer.
Q. (BY MR. JAMES) Do you know Dr. Hal Lawrence?
A. I do. Blue-eyed boy.
Q. Have you reached out to him with any concerns about the statement and how --
A. No, I have not.
Q. -- it's phrased?
MS. O'DELL: Dr. Smith, let him finish, please, with his question --
THE WITNESS: Oh, I'm sorry.
MS. O'DELL: -- just so it's clear on the record.
MR. JAMES: Okay. I'm about to the breaking point, I believe. I'm gonna mark as the next two exhibits, Exhibit 12.
THE WITNESS: I'm out of order.
MS. O'DELL: That's okay. We'll do it a --
THE WITNESS: I don't want to lose any. I don't.
MS. O'DELL: They're all there.

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THE WITNESS: Here. I got some over here. Sorry.
(Deposition Exhibit 12 marked for identification.)
Q. (BY MR. JAMES) All right. Dr. Smith, what I've handed you is the publication of risk factors for ovarian cancer published by the SGA -- SGO.
A. Yes.
Q. Just for the record, Dr. Smith, is this the list that you consulted in forming your opinions in this case?
MS. O'DELL: Object to the form; misstates her testimony. I think she said she didn't consult the list.
A. Yeah, I didn't read this for writing my report.
Q. (BY MR. JAMES) Okay. I thought earlier you testified --
A. I've looked them up.
Q. -- that you -- I'm sorry. Well, we're so close.
A. I interrupted you. I'm sorry.
Q. No. We're both doing it now, but we're

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close.
I'm sorry. I thought you acknowledged earlier that you were aware that talc was not listed as a risk factor on -- on the SGO's list.
MS. O'DELL: That's a different question, Counsel, but --
A. Yes, sir, I was aware of that.
Q. (BY MR. JAMES) Okay. So at some point you've read the list, correct?
A. Yes.
Q. Did you -- have -- when is the last time you've read the list?
A. I -- the last time I read the list was probably in the past two weeks. I did not use this list in the preparation of my report. I didn't use this as a source.
Q. And you didn't cite to it?
A. And I didn't cite it.
Q. And you didn't discuss it at all?
A. And I didn't discuss it at all.
Q. You agree it's relevant when opining on what risk factors are generally accepted, correct?
MS. O'DELL: Object to the form.
A. (Examined exhibit.) I'm sorry. I was

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reading it.
MS. O'DELL: Take a moment if you need to, Doctor, to read it.
A. (Examined exhibit.) I see something here that I can say is not permanent -- is not -- I disagree with. Let's put it that way. I disagree with.
Yes, women who -- yes. I mean, age is -- you know, when -- when you read all these papers on risk factors, aging is a risk factor for the development of ovarian cancer, and this is one of the few places that I say -- that I see actually say, "Yeah, the older you get, the higher your risk," because that's just the way it is.
They say women who have had gynecologic surgery makes them at increased risk for ovarian cancer, and I have never seen that before. I -- I can't remember seeing that anywhere.
And I've certainly seen hysterectomy decreases value and tubal ligation decreases value, but having that in the increase, that is not something I've ever seen. I'd like to see the studies that show that.
Okay. So my comments are done.

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Q. And before we break, Doctor, just for purposes of the record, I also want to confirm: At some point, you have looked at a list of risk factors for ovarian cancer published by ACOG, correct?
A. Yes.
Q. And earlier you acknowledged that talc was not listed on that --
A. Yes.
Q. -- list, correct?
A. Yes.
Q. And so I'm -- it's -- and, again, it's something that you have not cited or discussed in your report, correct?
A. (Nodded head.)
Q. So I'm going to hand you what I'm marking as Exhibit Number 13 to confirm that this is, in fact, what you've looked at. Okay?
(Deposition Exhibit 13 marked for identification.)
A. (Examined exhibit.) Okay.
Q. (BY MR. JAMES) Does that list -- does that publication that I've handed you look familiar to you?

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A. Yes.
Q. Is that what you reviewed before, Dr. Smith --
A. I've seen it before.
Q. -- with respect to ACOG?
A. I've seen it before.
Q. Do you consider it relevant to the opinions that you're offering in this case?
A. It is relevant to the conversation.
Q. Is it relevant to an opinion about whether something is generally accepted or not?
MS. O'DELL: Object to the form.
A. It's accepted by the members of -- or at least the steering committee of ACOG, and I -- this is pretty bland. It's -- I think most people would agree with these risk -- risk factors.
MR. JAMES: Is now time for a break everyone?
THE WITNESS: I'm up for it.
THE VIDEOGRAPHER: Going off the record. The time is 12:54 p m.

(A lunch recess taken from 12:54 p m. to 2:03 p m.)

AFTERNOON SESSION
THE VIDEOGRAPHER: Back on the record. The time is 2:03 p m.
EXAMINATION (CONTINUED)
BY MR. JAMES:
Q. Dr. Smith, are we ready to proceed?
A. We are.
Q. Great.
In compiling your list of generally accepted risk factors, did you consult the NCI's list of risk factors for ovarian cancer?
A. I did not.
Q. Okay. Are you aware that the NCI has listed risk factors in the publication referred to as the PDQ?
A. I know they have PDQs. I have not read that PDQ.
Q. You recognize the NCI, the National Cancer Institute, as a respected scientific organization?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) And I've seen references to the NC- -- NCI in your report, correct?
A. Yes.

Q. And they're a frequent sponsor of studies and --
A. Yes.
Q. -- cancer research, correct?
A. Yes.
Q. I'm gonna mark as Exhibit Number 14 the NCI PDQ on Ovarian Cancer Prevention, Health Professional Version.
(Deposition Exhibit 14 marked for identification.)
Q. (BY MR. JAMES) And, Dr. Smith, is this the first time that you've seen this document?
A. I believe so.
Q. Okay. If you turn to -- unfortunately, it's not paginated. I'll do a manual count for you.
If you flip seven pages and look on the backside of this double-sided copy.
A. (Complied.) Okay.
Q. Okay. At the top of that page there's a section titled, "Factors With Inadequate Evidence of an Association Risk of -- of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer."
Do you see where I'm reading?
A. Yes. And do you know what, I recognize

this page. I have seen it before.
Q. So you've seen this PDQ document?
A. Yes, I have.
Q. And this document is not cited or discussed in your report, correct?
A. It is not.
Q. Why is that?
A. I prefer to use peer-reviewed references rather than organizational websites or PDQs.
Q. And you reference other organizations in your report, correct?
A. Give me an example.
Q. For example, do you reference IARC in your report?
A. Oh, yes.
Q. Okay. But here you decided not to recognize the NCI PDQ, correct?
MS. O'DELL: Object to the form.
A. I think they're a different level of -- of standard between IARC and the PDQ.
Q. (BY MR. JAMES) Are you familiar with the process employed to prepare the PDQ that's in front of you right now?
A. I do not know what method that is.

Q. We see here on this PDQ on the page that I referred you to --
A. Um-hum.
Q. -- that below the category of "Factors With Inadequate Evidence," you see there that "Perineal talc exposure" is listed, correct?
A. Yes.
Q. Okay. And can you read that first sentence for me in the section right there?
A. "The weight of evidence does not support an association between perineal talc exposure and an increased risk of ovarian cancer."
Q. And your litigation opinion offered here today is different than what the NCI states here, correct?
A. Yes, it is.
Q. In determining whether something is generally accepted, do you believe it would be appropriate to consult what the National Cancer Institute says with respect to the association between ovarian cancer and talc?
MS. O'DELL: Object to the form.
A. I have told you that I have seen this and I looked at the references they cited, which is a

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very limited portion of the medical literature.
This is not an exhausted list of references. Certainly it lacks the most recent meta-analyses, so I think they didn't look at enough stuff.
Q. (BY MR. JAMES) Do you think the recent meta-analyses are the -- are pieces of literature that are critical to the causation opinion -- opinion you're reaching here today?
MS. O'DELL: Object to the form.
A. I believe they are more comprehensive and highly supportive.
Q. (BY MR. JAMES) And the question that I asked earlier, I think that maybe I didn't get an answer to.
Do you believe when opining about whether something is generally accepted it would be appropriate to consult what the National Cancer Institute has to say about the topic?
MS. O'DELL: Object to the form.
A. I've read it. It's not worthy of citation.
Q. (BY MR. JAMES) Do you believe the opinion published by the NCI with respect to risk factors

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and ovarian cancer is informative to your opinion about what is generally accepted as a risk factor for ovarian cancer?
MS. O'DELL: Object to the form.
A. I sought other references in peer-reviewed journals to compile my risk factor list.
Q. (BY MR. JAMES) Do you believe the NCI PDQ paper is relevant to forming an opinion about what is generally accepted by the medical community?
MS. O'DELL: Objection --
A. It is not relevant --
MS. O'DELL: Excuse me. Objection; asked and answered.
A. It is not relevant to my opinion because it is not comprehensive.
Q. (BY MR. JAMES) And when you say it's not relevant to your opinion, are you speaking about your opinion on causation?
A. Yes.
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) And --
A. Well, and risk factor. Yes, all of it.
Q. But in your report you've -- in addition to opine -- opining that talc is causative of

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ovarian cancer, you have also opined that talc is a generally accepted risk factor for ovarian cancer.
Do you understand the distinction between those two opinions?
MS. O'DELL: Objection to form.
A. I understand the difference in -- of those opinions.
Q. (BY MR. JAMES) And with respect to the latter opinion, the opinion about what is generally accepted by the medical community, would you agree that the statement provided by the NCI in its PDQ is relevant to determining what is generally accepted as a risk factor?
MS. O'DELL: Object to the form.
A. I don't -- I don't think that physicians go to the PDQ and say, "If that's what the NCI says, that's what I believe."
To find out the number of, for example, obstetricians/gynecologists who believe talcum powder products are a significant contributor to ovarian cancer, I believe to answer that question, we'd have to survey those people.
Q. (BY MR. JAMES) I think I've asked my question enough times there.

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What risk factors for ovarian cancer do you believe have been scientifically demonstrated to be synergistic or additive?
MS. O'DELL: Object to the form.
You may answer.
A. BRCA and -- BRCA 1 and 2 status in oral contraceptive use has been demonstrated to be additive.
Tubal ligation with nulliparity and other higher risk factors.
The -- I'm looking up the name of the author again.
MS. O'DELL: What are you referring to, Dr. Smith?
(Deposition Exhibit 15 referenced.)
A. The multiple risk factor studies of Vitonis, Titus-Ernstoff, and Cramer, 2011 and their five risk factors, one of which was talc, were cumulative in increasing your risk for -- as a scoring system for increasing your risk of ovarian cancer, so that's clearly an additive study. It doesn't look at synergy.
Q. (BY MR. JAMES) So the Vitonis study that you mentioned you're saying looks at cumulativeness,

but not synergy, correct?
A. Synergy to me means you put two things together and they're bigger than their sum. And I haven't seen that in ovarian cancer risk factors.
Q. As a whole or with respect to talc?
MS. O'DELL: Object to form.
A. As a whole.
Q. (BY MR. JAMES) So you don't have an opinion that -- let me start over.
Are there any ovarian cancer risk factors that you believe have been scientifically demonstrated to be synergistic?
A. I can't think of any at this time.
Q. Are there any risk factors for ovarian cancer that you believe have been scientifically demonstrated to be additive?
A. Yes.
Q. And what are those?
MS. O'DELL: Objection; asked and answered.
A. I just answered that question.
THE WITNESS: May I see the Vitonis paper, please?
MS. O'DELL: Sure.

MR. JAMES: I'm gonna mark the Vitonis paper as Exhibit 15.
(Deposition Exhibit 15 marked for identification.)
(Discussion off the record.)
Q. (BY MR. JAMES) Before we dig into the paper, Dr. Smith, and this may help move us along, in your report, you used the terminology "cumulative," "additive," and "synergistic."
A. I do.
Q. So synergistic we have discussed already, correct?
A. Correct.
Q. Do you believe "cumulative" and "additive" mean the same thing?
A. Not necessarily.
Q. Do you believe that it has been scientifically demonstrated that talc is cumulative with other risk factors?
A. I'm not aware of such a paper.
Q. Do you believe it has been scientifically demonstrated that talc is additive with other risk factors?
A. I believe this paper suggests it's

additive.
Q. And so this paper is discussing a hypothesis, correct?
MS. O'DELL: Object to the form.
A. That this paper has attempted to develop a risk factor score that may estimate patients who do not have documented genetic predisposition to ovarian cancer, so eliminating that possibility.
And now -- or they're trying to develop a risk factor based score system to advise physicians on when to include oophorectomy with hysterectomy and salpingectomy.
Q. (BY MR. JAMES) If you look with me at the first page in the Conclusion section of the abstract, Dr. Smith --
A. Um-hum.
Q. -- do you see there where it says that "We developed a risk-assessment tool that can quantify women's risk for ovarian cancer and should be validated in other data sets."
Do you see that language?
A. Yes.
Q. Okay. Do you acknowledge that this paper represents a hypothesis?

MS. O'DELL: Object to the form.
A. I -- it has not been validated by other studies that I am aware of.
Q. (BY MR. JAMES) Okay. Dr. Smith, on page 9 you begin your review of the epidemiologic literature, correct?
A. Yes, sir.
Q. Okay. And I'm referring you there because we'll spend a little bit of the time walking through it together. Okay?
A. Okay.
Q. You start your analysis with a discussion of meta-analyses in the pooled study, correct?
A. Correct.
Q. What limitations do you believe there are with meta-analyses in general?
A. Meta-analyses are statistical studies of single -- single site epidemiologic studies, but they are still retrospective in the tiers of level of evidence in medicine, case control, and cohort studies.
All epidemiologic studies are all listed at Level 4, which is obviously not the highest level of evidence. So that's a big

limitation to start with.
Q. Any other limitations that you can identify, sitting here today, with respect to meta-analyses?
A. I am not an expert on statistical methods, but I know there are multiple different statistical tools to perform meta-analyses, and I'm sure a biostatistician could give you a better discussion of that.
Q. So on page 9, you start with your discussion of the 1992 Harlow meta-analysis, correct?
A. Correct.
Q. How would you characterize the odds ratio reported in that meta-analysis?
MS. O'DELL: Object to the form.
A. It's -- the authors conclude there's associated, albeit modest, between ovarian cancer and peritoneal talc use.
In their study, their meta-analysis was 1.5, 0.9; but in all studies involved for 1100 patients, which is still a really small number, it's 1.3, confidence intervals 1.1 to 1.6.
Q. (BY MR. JAMES) And just to be clear,

Dr. Smith, the meta-analysis odds ratio for this paper is -- the crude odds ratio is 1.3, correct?
MS. O'DELL: Objection to form.
A. Yes, but it says "all studies."
THE WITNESS: Do you want to pull this out --
MS. O'DELL: Um-hum.
THE WITNESS: -- so I can --
MS. O'DELL: Sure.
THE WITNESS: -- look at it?
MR. JAMES: Leigh, I probably have it as well.
Did you beat me to it?
THE WITNESS: Yep. Well, she did. I didn't.
MS. O'DELL: I was trying to redeem myself from not alphabetizing correctly before.
Do you want to mark it, and I'll --
MR. JAMES: Sure.
BY MS. O'DELL: -- have to hand it to her.
MR. JAMES: I'm gonna mark the Harlow '92 study as Exhibit 16.
A. Let me go to this one. Easier for --

(Deposition Exhibit 16 marked for identification.)
Q. (BY MR. JAMES) And, Dr. Smith, just -- just to make sure we're framed correctly here, my question to you is: How you would -- how would you characterize an odds ratio of 1.3?
MS. O'DELL: Objection to form.
A. Depends on what the confidence intervals are, but it's -- it reflects a 30 percent increase in whatever you're measuring.
Q. (BY MR. JAMES) Would you characterize the association as weak?
MS. O'DELL: Object to the form.
A. 30 percent. It's relative. 30 percent more ovarian cancer is not weak. It's fatal.
Q. (BY MR. JAMES) That's not the question that I asked.
The question I asked is --
A. I wouldn't call it weak.
MS. O'DELL: Excuse me. Sorry.
THE WITNESS: Sorry.
MS. O'DELL: Let him finish and let me object. Go ahead.
Q. (BY MR. JAMES) How would you characterize

the 1.3, please?
A. 30 percent.
Q. Would you characterize it as a strong association?
A. I would characterize it as statistically significant number.
Q. Would you characterize it as a modest association?
A. Modest, weak suggests unimportant, and I would not call it unimportant.
Q. Do you understand that the authors of this paper use the terminology "modest"?
A. Yes, they did.
Q. Okay. Do you think that when they use that terminology they were calling it unimportant?
A. I think that they suggested that it was small in size. Small increase, modest increase, that's what they were meaning.
Q. And you understand one of the factors that experts use in evaluating an epidemiological body of literature is the strength of an association, correct?
A. Yes.
Q. And you discuss that later in your report,

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correct?
A. I do.
Q. And so my question here is whether, in your expert opinion, a 1.3 odds ratio can be characterized as strong, modest, weak, or another adjective?
MS. O'DELL: Object to the form.
A. I will use the authors term as modest. I'll accept that word.
Q. (BY MR. JAMES) Would you also accept the terminology "weak," if the authors use that term?
A. Did they use that term? Can you show me where they use the word "weak"?
Q. You can turn to the last page. Usually I'm asking questions, but I'm happy to try to point you out to what I'm discussing. Page 26 of the Harlow paper.
A. Um-hum.
Q. Okay. Do you see the last paragraph there?
A. Yes.
Q. That first sentence?
A. Oh, they did use the word "weak." If the authors use it, I will quote them.

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Q. Will you accept that terminology to describe the 1.3?
MS. O'DELL: Object to the form.
A. I -- in light of the larger body that's coming up, I will not accept that.
Q. (BY MR. JAMES) You --
A. That's my personal opinion.
Q. Is your personal opinion guided by principles of epidemiology?
MS. O'DELL: Objection to form.
A. Yeah, I think so.
Q. (BY MR. JAMES) You disagree with the characterization of the association by the authors of the study that you cite, correct?
MS. O'DELL: Objection; asked and answered.
A. Happens, yes.
Q. (BY MR. JAMES) Okay. Dr. Smith, looking at your report, returning to the second study that you cite, you cite the Gross and Berg study; is that correct?
A. I do.
Q. That's from 1995, correct?
A. It is.

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Q. Okay. And here you note in the report, if you turn the page, Dr. Smith, you have copied in a table from the article, correct?
A. Correct.
Q. In here, we see that according to your report the odds ratio is a 1.29, correct?
A. It is.
Q. And, again, how would you characterize a 1.29 odds ratio?
A. A 29 percent increase in ovarian cancer after talc exposure.
Q. And would you characterize that association as strong, modest, weak, or another adjective?
MS. O'DELL: Object to the form.
A. Are those my only choices?
Q. (BY MR. JAMES) No, I gave you another adjective choice at the end of my question.
MS. O'DELL: Objection.
A. You gave me strong, modest, weak.
Q. (BY MR. JAMES) I'm sorry if I -- maybe I misspoke, but I'm just asking you if you'd characterize a 1.29 as strong, modest, weak, or choose another adjective if you'd like.

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MS. O'DELL: Object -- excuse me. Object to form.
A. Statistically significant.
Q. (BY MR. JAMES) Would you acknowledge that there are statistically significant associations that in epidemiological community would be referred to as weak?
MS. O'DELL: Object to the form.
A. The rate of dissolution of an aspirin tablet in the stomach, coated or noncoated, in terms of time to analgesia may be statistically significantly different if there's a 30 second difference between coated and noncoated.
But that is a statistical significant difference that I find is not clinically significant. Whether your headache goes away 30 seconds sooner or later isn't clinically significant to me; whereas, a 29 percent increase risk of ovarian cancer is very clinically significant to me.
Q. (BY MR. JAMES) Do you understand that epidemiologists judge odds ratios based upon their strength?
MS. O'DELL: Object to the form.

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A. They may use adjectives to quantitate the amount of difference in terms of size or strength and they may use words "modest." I understand they do that.
Q. Do you understand --
MS. O'DELL: Excuse me.
Are -- I'm sorry. Are you finished, Dr. Smith?
THE WITNESS: Yes.
Q. (BY MR. JAMES) Do you understand that in judging associations, epidemiologists -- do you have expertise in epidemiology, Dr. Smith?
A. I do not.
Q. You do not?
A. Just reading them; not doing them.
Q. Do you understand that the weaker an odds ratio for an epidemiologist, that that bears some significance to an epidemiologist in making a causal conclusion?
MS. O'DELL: Object to the form.
A. It is one of Bradford Hill's nine factors or pos- -- he did -- didn't want to call them postulates.
One of Bradford Hill -- I forget the

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word he used -- nine factors in assessing causation and significance of epidemiologic findings.
Q. (BY MR. JAMES) Do you agree that when an association is lower, weaker, smaller, or more modest, that the smaller, weaker, or more modest that it gets, even if it's statistically significant, the lower the odds ratio becomes the more concerned you become as an epidemiologist or as an expert with whether that association is due to chance, bias, confounding?
MS. O'DELL: Obj- --
Q. (BY MR. JAMES) Do you accept that?
MS. O'DELL: Excuse me. Objection to the form.
A. It depends. It depends on if this is a single study, a small-numbered study, or whether that small result is consistent, reproducible over a wide number of studies.
Q. (BY MR. JAMES) Would you agree that the smaller the association the more concern there is -- there -- there is with confounding, chance, or bias?
MS. O'DELL: Excuse me. Objection; asked and answered.
A. Not necessarily.

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Q. (BY MR. JAMES) All right. The next study you discuss. And we're still on page 10, Dr. Smith, is the Cramer 1999 study.
A. Yes.
Q. And, I believe, just like with the prior, you have copied in a table from that study, right?
A. Once you learn it on the computer, you just keep doing it.
Q. Sure. And do you see there with the table that you've inputted into your report the odds ratio, a summary odds ratio of 1.4; is that right?
A. I do.
Q. Again, if the authors referred to that association in the paper as a relatively weak odds ratio, would you accept their terminology?
MS. O'DELL: Do you happen to have that paper handy?
THE WITNESS: You seem to be getting there faster than we are.
I'm missing 14. Where did 14 go?
Q. (BY MR. JAMES) I'll mark it as Exhibit -- I think we're at 17?
(Deposition Exhibit 17 marked for identification.)

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THE WITNESS: Are you get -- are you going -- I'm missing some of your exhibits.
MS. O'DELL: We'll -- we'll straighten it out.
THE WITNESS: Okay. I'm not responsible for that?
MS. O'DELL: You are not responsible.
THE WITNESS: Okay. I will quit worrying about it.
And I dropped my mike. I'm sorry. Can you still hear me, sir?
THE VIDEOGRAPHER: I can hear you.
THE WITNESS: Okay.
A. Yes, he does use "the relatively weak odds ratio observed."
Q. (BY MR. JAMES) Would you agree with that conclusion in the study that you cite?
A. As an epidemiologist, I think he's using epidemiologist speak. It's not my word choice.
Q. You are here evaluating a body of epidemiologic literature, correct?
A. I am. As a clinician and expert on ovarian cancer.
Q. And do you see here where the authors of

this article that you cited say in that same paragraph, quote, "Despite the consistency noted above, the relatively weak odds ratio observed could reflect potential biases, especially recall and confounding"?
A. Yes. And then they go on to say: (Paraphrasing.) Recall bias seems more likely to affect exposures that occurred over a short period of time than those occurred long ago. The average duration of talc exceeded 20 years in both cases, genital talc exposure may be less likely to be subject to recall bias.
And I cite that exact thing in quotations in my report. It is restated on page 356, I believe.
Q. So that you cite the portion of the statement that you read, correct?
A. Correct.
Q. Okay. But you didn't cite the statement that I read into the record, correct?
MS. O'DELL: Object to the form.
A. Correct.
Q. (BY MR. JAMES) Did you cite the portion of this -- of the article that supports your

opinion?
MS. O'DELL: Objection to the form.
A. I sub- -- quoted the part of the paper where the author specifically addressed concerns about recall, bias, and found them unlikely. I think it's important that he thought of it. I think it's real important that he thought of it.
But I think he, and every author, in every study should go through his or her study with a fine-tune comb that says "What -- "Why should I believe these results?
"What could I -- how -- what could I have made a mistake?
"What are confounding factors?
"Where is the bias that could've been introduced?
"Did I draw my conclusion from the data in my study?"
That's what every good author does, and so he did that. And then he answered his own question, "No, I don't think that's a confounding factor."
Q. (BY MR. JAMES) In discussing this study, do you discuss Dr. Cramer's findings on dose

response in your report?
A. (Examined exhibit.) He -- I do not discuss it in my report. He himself called dose-response relationship, quote, "weak," unquote.
Q. And you would agree that's an important finding of the study, correct?
A. I think you ought to look at every study to see if it has a dose-response relationship.
Q. Including this one, correct?
A. Every study. Yes, including this one.
Q. All right. Next, Dr. Smith, you discuss the Huncharek study, correct?
A. Correct.
Q. And in the text --
THE WITNESS: Are you just going to supply that to us?
MR. JAMES: I can or the --
THE WITNESS: I'd like to have the studies as we discuss them, if you wouldn't mind.
MR. JAMES: Absolutely. And -- absolutely.
And right now, I'm looking at your report with you as well, so . . .
THE WITNESS: Sure. Sure. But they

have -- I -- mine is a summary. You got the real thing.
MR. JAMES: Sure. As do you. But I'm happy to give you my copy.
THE WITNESS: Well, Ms. O'Dell does not mind getting every study for us. She's . . .
MR. JAMES: All right. So I'm going to mark the Huncharek study as Exhibit Number 18.
(Deposition Exhibit 18 marked for identification.)
A. Thank you. (Examined exhibit.)
Q. (BY MR. JAMES) And you note in your report an odds ratio of 1.33, correct?
A. Yes. Ever versus never exposure, "Relative risk of 1.33 with a 95% confidence interval of 1.16 to 1.45, a statistically significant result suggesting a 33% increased risk of ovarian cancer." That is a quote from the study.
Q. Dr. Smith, would -- how would you characterize a 1.33 odds ratio?
A. 33 percent --
Q. Okay. And would --
A. -- clinically significant, statistically significant.

Q. You recognize that all statistically significant associations cannot be described as strong, correct?
A. No. We've been through this.
MS. O'DELL: Objection to form.
A. Not all statistical significant -- you used the word "strong." I used the word "clinically significant." Those are different things.
Q. (BY MR. JAMES) I agree with you. And I'm asking you about strength.
MS. O'DELL: Could you repeat your question, please?
MR. JAMES: I'd be happy to.
Q. (BY MR. JAMES) Would you characterize the odds ratio in this paper as strong, modest, weak or another adjective that you prefer?
MS. O'DELL: Object to the form; asked and answered.
MR. JAMES: It hasn't been asked.
A. Clinically, statistically significant. That's the word I'm gonna use.
Q. (BY MR. JAMES) Is there a reason why you're uncomfortable characterizing the odds ratio with one of the adjectives strong --

A. That, yeah --
Q. -- modest or weak?
A. -- epidemiologists use because weak in -- I'm not an epidemiologist. Perhaps I don't have the epidemiologic --
(Counsel conferring off the record.)
A. Do you want me to wait while y'all talk?
Q. (BY MR. JAMES) No, ma'am.
A. I don't know the connotations of what "weak" means in epidemiologic circles. If it just means a small number, less than 2.0, weak, in my medical clinical brain implies unimportant, trivial. And I think that kind of difference, when you talk about ovarian cancer, is not trivial and it's not unimportant.
So maybe that's my hang-up, and maybe it's because I'm not an epidemiologist. I'm a -- I am person who takes care -- or took care of patients with ovarian -- continues to take care of people with ovarian cancer.
Q. You include the statement in your report that "The study" -- and I'm looking at your report now -- "did not collect the necessary data to permit this determination," in what you're referring to

there as dose response in the above sentence.
Do you see where I've --
A. Yes.
Q. -- read that?
A. Yes.
Q. Okay. And what's your basis for that statement?
A. This is -- I believe this is an ever/never study. Now, have you -- so if it's ever/never, you didn't use it or you ever used it. And so you -- implicitly, you can't get dose response if you don't look at frequency and duration. And a lot of these talc studies are ever/nevers.
Q. And this is not an attempt for a gotcha or anything like that, but I want to make sure we're looking at the same paper.
So can you turn with me to page 1958?
A. (Complied.)
Q. And you see Table 2. There's a table there with dose response data.
A. (Examined exhibit.) Well . . .
Q. Do you see here that the --
A. Yeah, I see --
Q. I'm sorry.

A. -- I see your table.
Q. Thank you.
A. I see your table. Here it's used. And I see what I wrote, and I haven't reread this immediately prior to my deposition.
MS. O'DELL: And if you need a few minutes to refresh yourself, Dr. Smith, feel free to do that.
THE WITNESS: I hate to waste your time, but I'd like to do that.
MS. O'DELL: Yes, please.
MR. JAMES: Yeah. Can we go off the record while the Doctor reviews the paper?
THE WITNESS: Sure.
MR. JAMES: Leigh, Margaret, is that fine?
MS. O'DELL: You know, if it's gonna take you a few minutes, I think --
THE WITNESS: Yeah.
MS. O'DELL: -- we'll go off. If it's gonna take you a minute or so, let's just give the Doctor a moment and we'll keep going.
THE VIDEOGRAPHER: Going off the record. The time is 2:44 p.m.

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(A recess was taken from 2:44 p m. to 2:56 p m.)
THE VIDEOGRAPHER: This marks the beginning of Disk 3. Back on the record. The time is 2:56 p m.
Q. (BY MR. JAMES) Dr. Smith, you've had a chance to look at the Huncharek paper, correct?
A. I have.
Q. And does that paper include data to permit a conclusion as to dose response?
A. It does not.
Q. And what's your basis for that statement?
A. They only had dose response information on 9 of the 16 studies, and the authors themselves said only a small minority of studies contain dose responses.
This is on page 1958, the left side column, second paragraph that starts there about halfway -- between one-third and one-half way down.
"Unfortunately, only limited data were available and only a small minority of" -- oh, I lost my place -- "only a small minority" --
UNIDENTIFIED SPEAKER: (Inaudible.)
THE WITNESS: Okay.

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A. -- "only a small minority of studies contain dose-response information of any type and (2), substantial differences existed in dose stratification levels among the studies reporting such information. It is therefore not possible to perform more sophisticated modeling of dose response data."
Final -- far- -- farther down on that, "The lowest half exposure category in this Cramer study was 'less than 30' applications, which is not consistent with other 'low.'"
"Taken together, these" -- last sentence, "Taken together, these data show a lack of clear dose-response relationship." Okay.
Q. (BY MR. JAMES) So you concluded your answer to my question with a sentence in the paper that says, quote, "Taken together, these data show a lack of a clear dose-response relationship," close quote, correct?
A. Correct.
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) So the authors have made conclusions about dose response, correct?
A. They can't. They said they couldn't. I

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must not be understanding you.
Q. Are you misunderstanding the paper?
MS. O'DELL: Objection to form.
A. No.
MS. O'DELL: She said she was misunderstanding your question.
MR. JAMES: I'm posing the questions, Leigh. Thank you.
Q. (BY MR. JAMES) Dr. Smith, you've stated in your report that, quote, "The study did not collect the necessary data to permit this determination," close quote.
Do you see that?
A. Yes.
Q. And your position is that the dose-response findings in this paper are a nullity? Is that your position?
MS. O'DELL: Object to the form.
A. I don't know what you mean by "nullity," but they didn't have sufficient data to determine a clear dose response.
Q. (BY MR. JAMES) Okay. And yet we do see here that the authors have made a conclusion about dose response, correct?

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MS. O'DELL: Object to the form.
A. "Despite the findings, the data showed a lack of clear dose-response relationship, making the relative risk of questionable validity." That's in their abstract.
So I don't see where they say they have made a clear dose-response relationship.
Q. (BY MR. JAMES) Okay. Let's just let the language of the paper speak for itself and we can move on.
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) Next you discuss the Langseth study, correct?
A. Yes, sir.
Q. And on page 12 of your report, you quote the statement in the paper, and I'm gonna mark it as Exhibit Number 19.
(Deposition Exhibit 19 marked for identification.)
Q. (BY MR. JAMES) Okay. I'm handing you a clean copy of Exhibit Number 19 of Langseth.
A. Thank you.
Q. Okay. In your report you quote the article for the proposition --

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A. You gave me two copies.
THE WITNESS: Does somebody else need another one?
Q. (BY MR. JAMES) -- for the proposition that the epide- -- "epidemiological evidence suggests that the use of cosmetic talc in the perineal area may be associated with ovarian cancer risk."
That's what you quote in your report, correct?
A. Correct.
Q. If you look at the second page of the article in the section titled "Proposal: To Research Community," do you see where I am?
A. I do.
Q. Okay. The authors there state, quote, "The current body of experimental and epidemiological evidence is insufficient to establish a causal association between perineal use of talc and ovarian cancer risk," close quote.
Do you see where I read that?
A. I do.
Q. And that conclusion of the author -- or the authors is not included in your report, is it?

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MS. O'DELL: Object to the form.
A. It is not. I don't agree with that conclusion.
Q. (BY MR. JAMES) So this is another paper that you've cited where you disagree with the authors' conclusions, correct?
A. Correct. They have a statistically significant overall risk of 1.35 -- between 1.26 to 1.46, so that is -- and then it says on research report what this study shows, "Epidemiologic [sic] evidence suggests the use of cosmetic talc in the perineal area may be associated with ovarian cancer risk."
Q. That's the portion that you've cited in your report, correct?
A. Yes, that is exactly what I quoted.
Q. But you didn't quote the sentence that I read that specifically disclaims a causal association, correct?
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) Or --
A. I --
Q. Well, let me --
A. I did not --

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Q. Sorry.
A. -- cite that.
Q. And, again, you -- in your report, you concluded that meta-analyses are -- I think you used the terminology "most valid" way to look at this issue; is that right?
A. Okay. I think they're the best we have, and I think they are the best we are going to have.
The best studies to determine causation are randomized, controlled, prospective trials, and more than one of them. That's what's called Level 1 evidence.
There is no ethical way we can apply any possible carcinogen, suspected carcinogen, proven carcinogen to the perineum of any woman and have that be ethically acceptable. That study cannot be done.
We are going to have to validate the epidemiologic data in the laboratory, because that's the only ethical place.
Q. And you understand the length of study is authored by the IARC Working Group, correct?
A. Yes.
Q. And do you understand that IARC has

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classifi- -- classified perineal talc application as a 2B?
MS. O'DELL: Objection to --
Q. (BY MR. JAMES) Do you understand that?
MS. O'DELL: Excuse me. Object to the characteration -- characterization regarding the working group.
A. IARC 93 classified talc as a 2B possible carcinogen.
Q. (BY MR. JAMES) Do you understand IARC has not classified talc as a carcinogen, correct?
MS. O'DELL: Object to the form.
A. Correct.
Q. (BY MR. JAMES) And IARC has not classified talc as a probable carcinogen, correct?
A. Correct.
Q. The conclusion that you're offering -- the opinion that you're offering here today conflicts with the IARC 2B finding, correct?
MS. O'DELL: Objection to form.
A. I told you that a study can't apply anything that's a possible, and I didn't say talc in any study.
I said the model for a randomized

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controlled trial would be apply whatever substance you want to women and see if they result in this disease.
But if you start with a possible, probable, or absolutely carcinogen, you're never gonna -- you can't -- you can't even write that down on the paper. That's not going anywhere.
That study will -- multiple studies we need -- we needed to have to have Level 1 evidence will never be done.
Q. (BY MR. JAMES) And I think that your answer maybe wasn't responsive to my question.
And so my question is whether the causation opinion you're offering in this litigation is different than the conclusion reached by IARC?
A. IARC in -- based on data up to 2006, declared talc a 2B possible carcinogen.
I believe that since 2006, in the past 12 years, we have a plethora of data that leads me to the conclusion that talc is a Class 1 carcinogen.
Q. You know IARC has not, to date, made that classification, correct?
A. That's right.
Q. Okay. Next in your report you discuss a

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Terry pooled analysis, correct?
A. Yes.
Q. And, again, here in your report -- and we can mark Terry if that -- I'll hand you a copy of that.
In your report you note the overall odds ratio in Terry is a 1.24, correct?
A. Yes.
Q. Okay. And I'm gonna mark Terry as Exhibit Number 20.
(Deposition Exhibit 20 marked for identification.)
Q. (BY MR. JAMES) You see here that the Terry odds ratio of 1.24 is lower than some of the odds ratios reported in the prior meta-analyses, correct?
MS. O'DELL: Object to the form.
A. Slightly. Well, let's see.
(Examined exhibit.) 1.33. 1.24 is smaller. Yes, I agree with -- that 1.24 is lower than 1.33.
Q. (BY MR. JAMES) Would you agree with the authors of this paper when they describe the odds ratio as a modest odds ratio?

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A. We've had this discussion before.
Q. Okay. Fair enough.
And your answers prior hold here as well?
A. They hold.
Q. Understood.
In your report, I didn't see any discussion in the -- when you're mentioning the Terry paper of the paper's findings on dose response.
Are you familiar with the dose-response findings in the Terry paper?
A. Once more, I'll need a moment to look.
(Examined exhibit.) They did -- there is no significant trend for increasing number of lifetime applications.
Q. And if you see on page -- I think you're reading on page 817; is that right, Dr. Smith?
A. I was reading from the abstracts.
Q. Oh, yes, Doctor.
If we also look at the page 812.
A. (Complied.)
Q. Do you see there where they say "Evidence for a dose-response relationship has been

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inconsistent" or are you on another page?
A. Did you say 812?
Q. Yes, Doctor.
A. The top?
Q. Yes, The top.
A. Yes. "Evidence of dose-response relationship has been inconsistent."
Q. And is there a reason why you don't discuss the dose-response findings of Terry in your report?
A. Because they didn't use -- they didn't observe the trend of increased risk applications. I mean, I -- it wasn't a pointed omission.
MS. O'DELL: If you want to re- -- need to review the paper.
Q. (BY MR. JAMES) Dr. Smith, are you reviewing or may I continue with another question?
A. Hold on one second. (Examined exhibit.)
Q. Sure.
A. (Paraphrasing.) No trend in cumulative use was evident in analyses restricted to ever-users of genital powder. Taken together, these observations suggest that the significant trend test largely reflects ever/never.

I would -- I would suggest that I didn't mention a negative. I mean, it isn't there.
Q. So that if a paper finds that there's no dose response, that's the basis for you not to report that finding?
MS. O'DELL: Object to the form.
A. I think it didn't add anything to the body of this report.
Q. (BY MR. JAMES) You acknowledge later in your report that whether or not the literature reports a dose response, one way or the other, is important to the causative analysis, correct?
A. I accept that it -- I could have improved my report by including that negative information.
Q. And if you look at the page 820 of the Terry article -- it's at the very end of the article. We see in the language at the top of the right column that the authors conclude, quote, "More work is needed to understand how genital powders may exert a carcinogenic effect, and which constituents (e.g., talc) may be involved."
MS. O'DELL: Object to form.
A. I would agree with that wholeheartedly.
Q. (BY MR. JAMES) So as of 2013, Dr. Smith,

the Terry authors are concluding that the -- concluding that whether or not talc exerts a carcinogenic effect is undetermined, correct?
MS. O'DELL: Object to the form; misstates the record.
A. That's what they stated, exactly. And I would agree more work needs to be done.
Q. (BY MR. JAMES) All right. Finally, Dr. Smith, you discuss the Penninkilampi --
A. Yes.
Q. -- study, correct?
A. Yes.
Q. I'm gonna mark the Penninkilampi study as Exhibit Number 21.
(Deposition Exhibit 21 marked for identification.)
Q. (BY MR. JAMES) In your report, Dr. Smith, you refer to the odds ratio with -- associated with long-term powder use as a 1.25, correct?
A. Correct.
Q. And if we look at Figure 2 of the study -- or it's Table 2 --
A. (Complied.)
Q. -- you see that the long-term use odds

ratio of the 1.25 is less than the overall odds ratio reported of the 1.31, correct?
A. I --
Q. And another -- maybe an easier place to reference, Dr. Smith, would be the abstract in the results section.
A. No. I believe I used the serous invasion rather than all. And that -- that's just -- I should've put "serous carcinoma" there, not "all." That's just a flat out mistake.
Q. And if we see in the Results section, Dr. Smith, we see -- and this is in the abstract portion of the paper, they report that the odds ratio with any perineal talc use associated with ovarian cancer --
MS. O'DELL: Where -- where are you reading from?
MR. JAMES: I'm in the abstract in the Results section.
MS. O'DELL: Okay.
MR. JAMES: This is 1.31.
A. Yeah. That's just a typo. Yeah, 1.31 --
Q. (BY MR. JAMES) And then --
MS. O'DELL: Excuse me.

Q. (BY MR. JAMES) Let me finish.
MS. O'DELL: Let him finish, please.
A. I'm sorry.
Q. (BY MR. JAMES) So the abstract reports that the overall odds ratio was a 1.31. But if you continue on reading in the abstract, you see that the long-term talc use odds ratio is a 1.25.
Do you see that?
MS. O'DELL: Object to the form.
A. Okay. How far down did you go? I see "any," then "more than 3600 lifetime applications" is 1.42.
And ever use is 1.35, 1.27, 1.43 in case control, but not cohort studies.
Q. (BY MR. JAMES) Okay. And my apol- --
A. "However" --
Q. Oh, sorry, Doctor.
A. -- is that where -- is that where you are? Is that the right sentence now?
Q. If -- if I may. If I may refer you back to Figure 2 and not Table 2, I think that will get us there quicker.
MS. O'DELL: I'm sorry, Scott. I'm sort of confused.

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MR. JAMES: Sure. And I'm gonna -- I'm straightening this up right now.
THE WITNESS: Okay. Okay.
Q. (BY MR. JAMES) So we're looking at Figure 2, which is where I initially --
A. Okay.
Q. -- tried to get us.
A. Okay. So -- okay. So the -- yes.
MS. O'DELL: Okay. Excuse me. Let him --
THE WITNESS: I'm sorry.
MS. O'DELL: -- ask a question.
Q. (BY MR. JAMES) So on page -- on Figure 2 --
MS. O'DELL: Excuse me. Dr. Smith, if you'll let him ask the question.
This is very -- gonna be very confusing on the record, so if we could just start over and make it clear.
MR. JAMES: Sure. Sure.
MS. O'DELL: Thank you.
Q. (BY MR. JAMES) So we're looking at the Penninkilampi study, Figure 2, page 46, correct?
A. Correct.

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Q. Okay. And do we see here, which is where I was trying to go, that the "Any perineal talc use" odds ratio reported here is a 1.31, correct?
A. Correct.
Q. And then they go on in Figure 2 to state that the "Long-Term perineal talc use" odds ratio is a 1.25, correct?
A. Correct.
Q. And the authors also note that it's a lower magnitude odds ratio, correct?
A. Correct.
Q. Does that lower magnitude odds ratio for long-term perineal talc use comport with your litigation opinions?
MS. O'DELL: Object to the form.
A. It's not inconsistent.
Q. (BY MR. JAMES) It's not inconsistent with your opinions that a long-term talc user has a lower odds ratio?
MS. O'DELL: Object to the form.
A. It is not unusual to have a -- a single inconsistent finding within one study. It doesn't change the whole picture of -- I mean, I note it. I acknowledge it.

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Q. (BY MR. JAMES) Uh-huh.
A. Cramer's got a paper. I think it's Cramer has a paper that tubal ligation increases ovarian cancer risks in one of his forms. I mean, it's -- you know, you have the outliers. But the body of literature doesn't support this single decrease from 1.31 to 1.25. But, you know, okay, but I see it. I know it.
Q. And in your report you discuss Penninkilampi as politically -- excuse me, particularly important to your analysis, correct?
MS. O'DELL: Object to the form.
A. I really like this study. I -- I like the scope of it. I like inclusion of the cohorts. It has a huge number of cases. Bigger is better. When you get away from small numbers and into the really large numbers, you have a much higher chance of finding truth if you -- so I like this study.
Q. (BY MR. JAMES) Do you see on page 42 of the study, it's the left-hand column, top paragraph, bottom sentence, the authors state, "Hence, while perineal talc use has not been shown to be safe, in a similar regard, a certain causal link between talc use and ovarian cancer has not yet been

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established," close quote?
A. They do say that.
Q. Okay. Do you agree with that finding or statement?
A. My conclusions are based on the totality of all the evidence that I have reviewed, not just the epidemiologic. Certainly, they have not reached that conclusion.
MR. KLATT: Objection; nonresponsive.
Q. (BY MR. JAMES) And the Penninkilampi authors did not reach a causation conclusion, correct?
MS. O'DELL: Object to form.
A. Well, in their introduction, they said a causal link has not been used.
And their discussion is that they said that a (paraphrasing) talc use appears to be associated with an increased risk of serous ovarian cancer, both invasive and borderline, and not with mucinous and with endometrial -- endometrioid ovarian cancer with perineal use.
Q. (BY MR. JAMES) The question remains, Dr. Smith: The Penninkilampi study that you cite as particularly important in your report, the authors

there do not render the conclusion that talc is a demonstrated cause of ovarian cancer, do they?
MS. O'DELL: Objection to form; asked and answered.
A. They ask for a sustained need for further research on the potential mechanism by which ovarian cancer may be caused by talc.
So they -- they do not allow a causal relationship, nor do they allow rejecting that causal relationship.
Q. (BY MR. JAMES) And here, we do know that you have rendered the causation opinion, and so your causation opinion is different than the opinion reached by the authors of the Penninkilampi study, isn't it?
A. Yes.
Q. When evaluating the Penninkilampi study, did you note that the Penninkilampi authors omitted certain cohort data?
A. They use Gertig rather than Gates.
Q. Okay. And the Gates paper is the follow-up paper, correct?
A. The Gates paper is the -- do you want to do the -- the prospective studies now or do you want

to do it as part of this?
Q. I -- right now, I'd just like to continue with the questioning.
A. Okay. Okay.
Q. And if there is a --
A. Okay.
Q. -- point where you'd like the papers, we'll get them for you.
A. Thank you.
Q. Okay.
A. I always love the papers.
The Gates study is the first half of the Nurses' study.
MS. O'DELL: Scott, if you're gonna mark the papers, why don't we go ahead and mark Gates and --
THE WITNESS: Gertig?
MS. O'DELL: -- if you're going to --
Yes.
If you're going to -- I think we've marked them --
MR. JAMES: Sure. That sounds fine.
MS. O'DELL: That way the Doctor can have it in front of her while she's answering the

questions.
MR. JAMES: Okay. So I'm marking the Gates 2010 paper as Exhibit 22.
(Deposition Exhibit 22 marked for identification.)
Q. (BY MR. JAMES) And so the question -- I'll rephrase.
MS. O'DELL: Oh. I thought you were gonna hand me something else. Okay.
Q. (BY MR. JAMES) The Gates paper is the -- is a paper produced on the Nurses' Health cohort, correct, Dr. Smith?
A. Did you say the Gates' paper?
Q. Yes.
A. Yes.
MS. O'DELL: Are you gonna mark Gertig, if you're gonna compare the two?
MR. JAMES: I'll mark Gertig as Exhibit 23.
(Deposition Exhibit 23 marked for identification.)
Q. (BY MR. JAMES) And Dr. Smith, Gertig is also a Nurses' Health paper, correct?
A. It's the first one.

Q. Thank you.
A. Thank you.
Q. All right. And so to reframe the question, Dr. Smith, the Penninkilampi study omits the data from the Gates 2010 study, correct?
MS. O'DELL: Object to the form. Excuse me. I'm sorry.
A. It used Gertig and not Gates.
Q. (BY MR. JAMES) Okay. Is there --
A. I -- I don't think he -- I don't know why he -- that is what it is.
Q. And, again, you understand the Gates 2010 paper has data on additional years of follow-up, correct?
A. And additional patients.
MS. O'DELL: Objection to form.
Q. (BY MR. JAMES) And you understand that the Gates 2010 paper includes an analysis of the odds ratios associated with talc and ovarian cancer, correct?
A. Correct.
Q. Do you believe the Penninkilampi study should have included the data from the Gates 2010 paper?

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A. I --
MS. O'DELL: Object to the form.
A. I believe it doesn't matter.
Q. (BY MR. JAMES) Why doesn't it matter?
A. Because we have the Berge study that did include it, and that -- for some reason, it's not included in my report, and if you don't call it a flaw, I will. I -- I think in multiple drafts and cut and pasting it went to the great cyber void.
Q. Okay. And that's -- the discussion that you just had was concerning the Berge paper, correct?
A. Right.
Q. But returning back to the Penninkilampi study, do you believe it was a flaw for the authors not to include data from Gates 2010?
MS. O'DELL: Objection to form.
A. No, I don't.
Q. (BY MR. JAMES) Why is that?
A. Because it doesn't make any difference. Because Berge did, and it didn't make any difference in the results.
Q. Okay. So I'm asking about the Penninkilampi study. And my question is whether

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Penninkilampi should have included the data from the Gates 2010.
MS. O'DELL: Object to the form.
A. Well, if you use the most recent available data, maybe he should have, yes, you're right.
Q. (BY MR. JAMES) And, in fact, that's one of the points that you make in your report, correct?
You -- one of the things you note in your report is follow-up is a good thing, right?
A. Correct.
Q. And the Penninkilampi authors make certain conclusions about the cohort data, don't they?
A. You're gonna have to tell me what those conclusions are before I'll agree with or not agree with that.
Q. Okay. Dr. Smith, if you -- do you have the Penninkilampi paper in front of you?
A. I do.
Q. Okay. And you see on page 47 in the Conclusions section --
A. Um-hum.
Q. -- you see that, quote -- and this is the second sentence down --
A. Um-hum.

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Q. -- "While the results of case-control studies are prone to recall bias, especially with intense media attention following the commencement of litigation in 2014, the confirmation of an association in cohort studies between perineal talc use and serous invasive ovarian cancer is suggestive of a causal association," closed quote.
Do you see that?
A. Yes.
Q. And so Penninkilampi is hinging its conclusions on what it believes to be the results of, quote, "cohort studies," closed quote, correct?
MS. O'DELL: Object to the form.
A. I don't believe that they hinge their whole findings on cohort studies. Their statistical and significant include- -- significance included those cohort studies, but it's only a component of theirs.
Q. (BY MR. JAMES) And certainly in the Conclusions section, the Penninkilampi authors acknowledge the bias limitations associated with case control studies, correct?
A. They say case control studies are prone to recall bias. I think a better choice of words would

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be may be prone to recall bias.
But, yes, cohort studies obviate recall bias. They don't have it.
Q. And we know again here that Penninkilampi did not include the Nurses' Health cohort data from 2010 Gates, correct?
MS. O'DELL: Object to the form.
A. Correct.
Q. (BY MR. JAMES) Okay. And are -- do you know that in the Gates 2010 paper the reported association with the serous ovarian cancer washed out?
A. I know that.
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) And Penninkilampi apparently doesn't know that, correct?
MS. O'DELL: Object to the form.
A. I haven't talked to him.
Q. (BY MR. JAMES) Okay. Well, Penninkilampi is referring to a confirmation of an association and cohort studies.
Do you see that?
A. Right.
Q. So he must be referring to --

A. The Gertig study.
Q. -- Gertig study, correct?
MS. O'DELL: Excuse me.
A. Right.
MS. O'DELL: Object to the form.
Hey, Doctor, give me just a minute to --
THE WITNESS: Okay. I'm sorry.
MS. O'DELL: -- get my objection in.
Q. (BY MR. JAMES) And we know that's true because we know none of the cohorts performed today have found an association, correct?
MS. O'DELL: Object to the form.
A. That is true.
Q. (BY MR. JAMES) We know the Women's Health Initiative study did not find an association between perineal talc use and ovarian cancer, correct?
MS. O'DELL: Object to the form.
A. That is true.
Q. (BY MR. JAMES) We know the Gonzalez Sister Study -- the prospective Gonzalez Sister Study did not find an association between perineal talc use and ovarian cancer, correct?
A. That is true.

Q. So we can deduce here that the only study that he can be referring to is the Gertig 2000 study, correct?
A. He lists Gertig in his reference -- in his -- see. He lists Gertig --
Q. So there's no dispute --
A. -- right there.
Q. I'm sorry, Doctor.
A. In Gertig, there's no dispute. He's not trying to hide anything. It's listed, "Gertig 2000."
Q. Right. So there's no dispute in our discussion here either that what he's referring to there is the Gertig 2000 study, correct?
MS. O'DELL: Object to the form.
A. He is referring to the Gertig.
Q. (BY MR. JAMES) And he just forgot to look at the Gates 2010 data, correct?
A. I don't know why --
MS. O'DELL: Object to the form.
A. -- he didn't look at the Gates study.
MS. O'DELL: Excuse me, Doctor.
Object to the form.
You may answer.

Q. (BY MR. JAMES) If you had looked at the Gates --
MS. O'DELL: Hey, let -- finish -- if you've got an answer --
Did you finish your answer?
THE WITNESS: I did finish my answer.
MS. O'DELL: Okay. Give me a moment. Thank you.
THE WITNESS: I know. I'm not supposed to talk so fast.
Q. (BY MR. JAMES) If you had looked at the Gates 2010 data, he wouldn't have been able to make that statement, correct?
MS. O'DELL: Object to the form.
A. Do you mean the statement that the confirmation of an association in cohort studies between perineal talc use and serous invasive cancer is suggested of a causal association?
Well, his -- the Gates study did not have statistically significant increase incidence of serous ovarian cancer.
Q. (BY MR. JAMES) Another reason that you'd want to look at the most recent data available from a cohort is because of concerns about latency, which

you also cite in your report, correct?
MS. O'DELL: Objection to form.
A. That's not the only reason to just look at most up-to-date studies.
Q. (BY MR. JAMES) Is it one of the reasons?
MS. O'DELL: Object to the form.
A. I have never con- -- thought about latency in terms of looking at the most recent study and the most up-to-date studies.
Q. (BY MR. JAMES) Okay. In your report, do you recall critiquing the cohort studies on the basis that, in your opinion, they have short follow-up and don't account for latency?
Do you recall that critique?
A. Particularly -- particularly the Gonzalez study, yes.
Q. Okay. But the -- the question that I'm posing here is more general in nature.
Is that one of the reasons that you would want to include the most recent data from a cohort is to, in part, address the concern of latency that you --
A. The longest follow-up possible.
Q. Okay. We will turn to the Berge study,

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which you previewed for us, Dr. Smith, and I will hand you a copy, if I haven't already.
MR. JAMES: I'm gonna mark Berge, B-e-r-g-e, as Exhibit 24.
(Deposition Exhibit 24 marked for identification.)
Q. (BY MR. JAMES) Dr. Smith, I've handed you the Berge paper.
And this is a paper you have seen before, correct?
A. It is.
Q. And as you just discussed, you acknowledge it's not discussed in your report, correct?
MS. O'DELL: Objection to form.
Q. (BY MR. JAMES) Or I'll -- I'm going to rephrase. I know -- I --
A. I have cited it --
Q. -- I can correct that.
You cited it for a publication bias point, correct?
A. I don't -- I'd have to look where I cited it.
Q. Okay.
A. I -- it's missing from here. Yeah.

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Q. Do you agree that you haven't discussed the Berge study in-depth in your report?
A. Correct.
Q. And that was a -- what you were alluding to earlier as a mistake and omission. Fair?
MS. O'DELL: Objection to form.
A. Correct.
Q. (BY MR. JAMES) What are your thoughts on the Berge study?
A. Again, it -- it -- it uses Gates instead of Gertig. It has very similar findings to Penninkilampi. If you look at his forest plot, he looks at the cohort studies: Gates, Houghton, Gonzalez, nurses, women, sisters. Again, they are not statistically significant on their relative risk and confidence intervals.
And yet in inclusion with the entire population, his numbers are very similar to Penninkilampi with an overall relative risk slightly lower of 1.22 versus Penninkilampi is 1.31; confidence intervals 1.13 to 1.30 for Berg remains statistically significant as Penninkilampi 1.24 to 1.39.
Q. Do you -- Doctor, are you finished?

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A. I was looking for something, but go ahead and talk.
MS. O'DELL: Excuse me. I think -- let me get -- I think maybe -- do you have part of the table missing from your version?
THE WITNESS: There's -- yeah, there's a table that I'm used to around here.
MR. JAMES: Do you have a better copy, Leigh?
THE WITNESS: Let me see.
MS. O'DELL: Is it an eTable?
THE WITNESS: No, I think it's just the copy . . .
MR. JAMES: That's all I have.
THE WITNESS: Oh, yeah. No. I don't know. Yeah, this is my copy.
MR. JAMES: Okay. Let me see.
And Mr. Klatt has handed me some better copies as well, if anybody needs a better one as well.
MS. O'DELL: Thank you.
MR. JAMES: And at the break, I will resticker.
THE WITNESS: Yeah, it's Table 2 on --

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here it is.
A. Table 2 on page 6 where Penninkilampi -- I am becoming buried -- found invasive serous.
So first, I'm gonna give you Penninkilampi's statistically significant increase rate invasive serous cancer with genital talc use. Penninkilampi's numbers are overall risk 1.25, confidence interval 1.01 to 1.55.
Berg -- Berge is 1.24, confident intervals 1.15 to 1.34.
So this is why I told you from comparing these two papers that Gertig versus Gates, when you look at all the same body, it's six of one half-a-dozen of the other, the inclusion of which of those two post -- his studies in meta-analyses.
Q. (BY MR. JAMES) But you have already agreed with me that it would have been better for Penninkilampi to included the Gates 2010 data, correct?
MS. O'DELL: Objection to form.
A. I like using the most recent study.
Q. (BY MR. JAMES) And that's EPI 101, isn't it?
MS. O'DELL: Objection; form.

A. That's everything 101.
Q. (BY MR. JAMES) And we see here in the Berge paper if we look at the conclusions in the abstract, the very last sentence of the paper, the authors conclude, quote -- and I'm at the very first page of the paper in the abstract -- they conclude, quote, "The heterogeneity of results by study design . . . however, detracts from a causal interpretation of the association."
A. I think I'm in the wrong place.
MS. O'DELL: What page are you on?
MR. JAMES: The abstract.
A. The heterogeneity.
Q. (BY MR. JAMES) Dr. Smith, I think your scarf is covering your mike.
A. I'm sorry. Nope. I broke it.
THE VIDEOGRAPHER: Okay. We need to go off the record.
MR. JAMES: Okay. Off the record.
THE VIDEOGRAPHER: Okay. Off the record. The time is 3:41 p m.
(A recess was taken from 3:41 p m. to 4:13 p m.)
THE VIDEOGRAPHER: Back on the record.

The time is 4:13 p m.
Q. (BY MR. JAMES) And, Dr. Smith, when we broke, we were discussing the Berge study, correct?
A. Yes.
Q. And so I'm gonna -- I think that when we broke I was pointing you toward the abstract portion of the patient -- paper.
A. Correct.
Q. Okay. And do you see there at the bottom of the abstract the authors there conclude, quote, "The heterogeneity of results by study design and the lack of a trend for duration and frequency of use, however, detract from a causal interpretation of this association," close quotes?
A. That --
MS. O'DELL: Object to form.
A. That was their assessment.
Q. (BY MR. JAMES) Okay. And your litigation opinion differs from the causal conclusions reached by these authors, correct?
MS. O'DELL: Object to the form.
A. My causal interpretation is built on the totality of all of these studies and the biochemistry and all the literature I reviewed. So

it does differ from this individual one paper.
Q. (BY MR. JAMES) And, again, the individual one paper you're here is a meta-analysis that -- it is a meta-analysis, correct?
A. Yes. I have -- I have great respect for this paper.
Q. And we see the -- in the conclusion that we just read, one of the points the authors here make concerns the heterogeneity results by study design, correct?
A. Correct.
Q. And there the authors are noting that the association that appears in a subset of the case control studies is not being replicated in the cohorts prospective studies, correct?
MS. O'DELL: Object to the form.
A. Case control studies are entirely different from cohort studies.
Q. (BY MR. JAMES) All right. Let me ask my question again.
A. Okay.
Q. Here when the authors are referring to the difference in the results of the types of studies, right, in this conclusion, that's what they're

referring to, aren't they, when they say "heterogeneity"?
A. I can't -- I can't define their heterogeneity.
Q. Let me try again. So here the authors refer to the -- quote, "The heterogeneity of results by study design," close quote.
Does that phrase -- do you understand what they mean by that phrase?
A. Do they define it further in the text? I don't remember that.
Q. Let's look to page 253 of the article.
A. Mine has single-digit page numbers.
Q. Hum.
A. Starts on page 1 and goes to page 9 -- oop. Because mine's an e-Pub. This is an e-Pub.
MS. O'DELL: This is the copy I think you gave.
MR. JAMES: Can I see that real quick?
MS. O'DELL: Yeah.
MR. JAMES: Is that an e-Pub as well, Leigh, on the front?
BY MS. O'DELL: It --
THE WITNESS: It says, "Cancer --

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General Cancer Position 00000."
MS. O'DELL: Is that the same one you're looking at? It's just different page numbers.
MR. JAMES: Um-hum.
MS. O'DELL: That may be the copy that -- I think that's the copy that -- that Mike gave us.
MR. JAMES: Um-hum.
THE WITNESS: Because on my copy, I had to write down the final publication information beside it.
MR. JAMES: Okay. I think on the next break I'm gonna take a peek closer at these Berge articles. I think we may still have a disconnect.
MS. O'DELL: Okay.
MR. JAMES: I'm not sure why we're looking at two different versions on the same paper. Here you go.
THE WITNESS: I have written here that the final publication pages were 248 through 257 of Volume 27.
Does that help you?
MR. JAMES: Sort of. So let's --

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let's just keep moving. Okay?
THE WITNESS: Okay.
MR. JAMES: Let's keep plowing.
Q. (BY MR. JAMES) The Berge authors made a conclusion that the evidence was insufficient to support causation, correct?
MS. O'DELL: Object to the form.
A. They say it detracts from causal interpretation of this association.
Q. (BY MR. JAMES) And one of the items they consider is the fact that the cohort data does not report a statistically significant association between ovarian cancer and talc use, correct?
A. Because they use Gates.
Q. Understood.
Would you agree that all of the meta-analyses that we have looked at today and that you addressed in your report are relying on a -- on a similar set of data?
MS. O'DELL: Object to the form.
A. I will certainly tell you the past three studies -- two to three studies we've looked at work on a similar data. This is a growing body of epidemiologic evidence, so each study grows in the

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number of studies they include.
Q. (BY MR. JAMES) So as time goes on and more studies are performed testing the hypothesis of ovarian cancer in talc, that body of literature can be included in the next meta-analysis that's completed, correct?
MS. O'DELL: Object to the form.
A. Correct.
Q. (BY MR. JAMES) You agree that the meta-analyses of all of the underlying studies cannot eliminate the recall bias in the underlying studies?
MS. O'DELL: Object to the form.
A. In any case control study, there exists the possibility of any recall bias.
Q. (BY MR. JAMES) And putting these studies together in a meta doesn't eliminate that, correct?
MS. O'DELL: Object to the form.
A. No, it does not.
Q. (BY MR. JAMES) And you may recall this, but the Penninkilampi study concedes that point, correct?
MS. O'DELL: Object -- object to the form.

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A. (No response.)
Q. (BY MR. JAMES) And Dr. Smith, referring to page 47, the Conclusions section of the paper.
A. Yes.
Q. And we see here that the -- if you look down to --
A. Yes.
Q. -- the last sentence in that column, they say, "Additional epi evidence from prospective studies with attention to effects of ovarian cancer subtype is warranted."
Do you see that?
A. I see that.
Q. And so the authors here in the Penninkilampi study are expressing a need for additional prospective data, correct?
MS. O'DELL: Objection.
A. Correct.
Q. (BY MR. JAMES) We've talked already, in some fashion, about the cohort studies.
You agree with me that the litigation opinions you're offering in your report conflict with the cohort studies, correct?
MS. O'DELL: Object to the form.

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A. The cohort studies, with the exception of Gertig and serous, showed no statistically significant increase hazard ratio or relative risk or standardized mortality ratio, depending on the statistics they chose, hazard ratios for ovarian cancer. That is a fact.
Q. (BY MR. JAMES) You discuss the Houghton study, the Women's Health Initiative study on page 15 of your report.
A. Yes.
Q. And you include the note that -- on page 15, that "No histologic information was obtained."
Do you see that phrase in your report?
A. I do.
Q. Do you believe that to be correct?
A. May I see the paper.
Q. Yes, Doctor.
MR. JAMES: I'm gonna mark the Women's Health Initiative Houghton study as Exhibit Number 25.
(Deposition Exhibit 25 marked for identification.)
THE WITNESS: Thank you.

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Q. (BY MR. JAMES) If we look at the study on page 3, Dr. Smith.
A. (Examined exhibit.) Yes. Table 1?
Q. You're ahead of -- you're ahead of me.
MS. O'DELL: Please wait for the question, Dr. Smith.
THE WITNESS: He said, "If we look at the study on page 3." That was a question.
Q. (BY MR. JAMES) Yes. Yes. Yes, page 3. Page 3. I'm getting there.
(Examined exhibit.) And the study states that "Associations by ovarian cancer histological subtype were evaluated."
A. I'm sorry. Where are you on page 3?
Q. Give me one second. I lost it. I'm on the wrong page here. Give me one second.
Dr. Smith, if we turn to page 5 of 6 --
A. Um-hum.
Q. -- we see here that there is information in the Table 4 pertaining to Histology, correct?
A. I see that.
Q. Okay. And do you know if this study found any variation in risk by subtype?

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A. They did not find any variation of risk by subtype.
Q. Okay. So would you agree with me, then, that that statement in your report is erroneous?
A. I believe --
MS. O'DELL: Object to the form.
A. I believe I -- it would have been better stated "No difference in risks by histologic information was demonstrated."
Q. (BY MR. JAMES) Okay.
A. What it stated here is wrong.
Q. Are your opinions that you're offering today on general causation between talc and ovarian cancer histologic specific?
A. With regards to mucinous ovarian cancer, I have seen no -- strike that.
I learned how to say that.
Q. That's fine.
A. With a totality of the information I've looked at, I do not believe talcum powder is a risk factor for the development of mucinous ovarian cancer.
Q. Do you believe it is a risk factor for the other subtypes of epithelial ovarian cancer?

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A. I am certain that it's a risk factor for the risk factor of serous invasive ovarian and endometrioid invasive --
Did I say endometrial?
Q. You did.
A. Oh, I meant -- okay. Let me start again.
I believe it is. It -- talcum powder products cause invasive serous ovarian cancer and invasive endometrioid ovarian cancer.
I am less clear on its relation to clear cell carcinoma, and I believe it is not a causative agent in the development of mucinous ovarian cancer.
Q. And when you say you're less clear with respect to clear cell, sitting here today, do you offer the opinion that talc is causative of clear cell ovarian cancer?
A. It is -- yes, I will say that. Because of the inflammation, yes, I can say that.
Q. So you're -- you say that you're less clear about it, but you still feel --
A. I think there's less dat- --
MS. O'DELL: Let him finish his question.

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Q. (BY MR. JAMES) So you --
THE WITNESS: Let him finish his question.
Q. (BY MR. JAMES) So you say that you're less clear about clear cell, but you were still comfortable stating that the evidence is sufficient to conclude that talc causes clear cell carcinoma?
MS. O'DELL: Objection; form.
A. I can say it better. Clear cell carcinoma is a less frequent histologic type, but inflammation still contributes heavily to its development. I think we have fewer cases; therefore, fewer data, but I think talc contributes to its development.
Q. (BY MR. JAMES) And when you say "contributes to its development" --
A. Causes.
Q. -- I think you --
A. In a legal term.
Q. -- are you asking -- are you saying that it causes?
A. Causes.
Q. So your opinion here today is that talc is causative of serous?
A. Serous.

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Q. Serous endometrioid --
A. Yes.
Q. -- and clear cell; is that correct?
A. Yes.
Q. Do you consider those three subtypes of ovarian cancer to be separate diseases?
MS. O'DELL: Object to the form.
A. If they're -- if they're poorly differentiated, they are in the same type 2 ovarian cancer that we talk about aggressive, metastasized widely, fatal, yes.
Q. (BY MR. JAMES) Do you believe that the risk factor profiles for serous, endometrioid, and clear cell are different or the same?
MS. O'DELL: Object to the form.
A. They're certainly overlapping. Endometriosis is generally associated more with endometrioid and clear cell carcinomas, less so with serous carcinomas.
Q. (BY MR. JAMES) If other experts have reached the conclusion that the association between talc and ovarian cancer is causative -- proven causative by the science only with serous and talc, then you would disagree with those experts?

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MS. O'DELL: Object to the form; lack of foundation.
A. I'd love to discuss it with them.
Q. (BY MR. JAMES) Do you have any quarrels with the analysis on the Houghton paper?
A. Could you be more specific?
Q. Do you have any critiques, just sitting here today, of the Houghton paper?
MS. O'DELL: Object to the form; vague.
A. Well, in evaluating it, I looked at that it was small and -- well, it's 61,000 postmenopausal women. It had a relatively short follow-up of only 12.4 years. The number of cases is low, about 429, so -- I mean, it's a small, short study.
Q. (BY MR. JAMES) (Short pause.)
And do you understand that the Women's Health Initiative included a question on duration?
A. Yes.
Q. Okay. Did you factor that into considering your comment on follow-up?
MS. O'DELL: Object to the form.
A. The follow-up's still 12.4 years. It

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doesn't change it.
Q. (BY MR. JAMES) Does the fact that they asked about duration factor into your analysis at all?
A. It's better to ask about duration, but --
Q. And -- I'm sorry.
A. -- but it doesn't change how long the study went on with the small numbers.
Q. And so the study, if -- by asking about duration is increasing data on the -- on the time period for which it's evaluating talc users, correct?
A. Correct.
MS. O'DELL: So off the mark. I object to that question.
Q. (BY MR. JAMES) On page 16 of your report, you state that, quote, "In my opinion, meta-analyses is the most valid and reliable way to study an issue like ovarian cancer," closed quote.
Did you see where I read that?
A. I see "In my opinion meta-analyses provides most reliable evidence in this situation."
Is there another place? That's the third -- second full paragraph.

I heard you say "valid," and I don't -- I'm not seeing that word.

MS. O'DELL: I think you need to look a bit further down the page.

THE WITNESS: Sorry.

MR. JAMES: Yeah.

Q. (BY MR. JAMES) It's the next paragraph.

Do you see that? It's the lead sentence --

A. Yeah, okay. I'm -- okay. I'm with you now.

Q. Okay. Is that statement confined to talc or to ovarian cancer in general?

MS. O'DELL: Object to the form.

A. No. I mean, if we're looking at treatment studies, we have the opportunity to do prospective randomized controls trials, like the Armstrong trial that's cited in here. Those are always the best forms we have for treatment. We just can't do it for exposure.

Q. (BY MR. JAMES) Here you say that you consider meta-analyses to be the most valid and reliable way to study an issue like ovarian cancer, correct?

MS. O'DELL: Object to the form; asked and answered.

A. I think meta-analysis is most valid and reliable way to study risk in ovarian cancer. Perhaps the word "issue" was not the best word choice.

Q. (BY MR. JAMES) So you believe that meta-analysis is the best way to study risk factors for ovarian cancer?

MS. O'DELL: Object to the form.

A. Yes.

Q. (BY MR. JAMES) Do you understand that the literature that we have discussed today, prospective cohort studies, meta-analyses, case control studies commonly make the comment about the advantages over -- excuse me -- the advantages of prospective studies over retrospective studies?

A. Absolutely.

Q. And those studies that make those comments are the studies that look at the issue of talc and ovarian cancer.

MS. O'DELL: Excuse me. Make --

Q. (BY MR. JAMES) Correct?

A. Are you talking about --

MS. O'DELL: Excuse me. Let me object to form of that question and the question before.

MR. JAMES: A retrospective objection.

MS. O'DELL: Yes, that's right.

A. Prospective what type studies, please?

Q. (BY MR. JAMES) Okay.

A. Cohort versus randomized? Double-blind?

Q. So the meta-analyses, for example, that you have described as the most valid and reliable way to study the issue have commented in the studies themselves that prospective data is a higher level of evidence.

Did you know that?

A. Are you talking about cohort studies that are prospective?

Q. Correct, prospective cohort studies.

A. Okay.

MS. O'DELL: Object to the form.

A. Which can be analyzed by meta-analysis as well.

Q. (BY MR. JAMES) But the meta-analyses themselves that you have cited have discussed --

A. Contain retrospective studies.

Q. Excuse me. Just one second.

The meta-analyses that you have cited and relied upon have discussed the fact that prospective cohort studies are higher level evidence.

Did you know that?

MS. O'DELL: Object to the form.

A. In general, I know that.

Q. (BY MR. JAMES) The cohorts themselves in their methodology sections and discussion sections talk about the fact that they are being studied prospectively for the purpose of eliminating recall bias.

Do you understand that?

MS. O'DELL: Object to the form.

A. That is one bias that can be eliminated in a prospective cohort study, but they're both Level 4 evident epidemiologic studies which comes fourth down the scale on the validity of scientific papers.

Q. (BY MR. JAMES) For example, the Houghton study that we've looked at today says that "The prospective nature of our study would eliminate the potential for recall bias."

Would you agree with that statement?

A. Yes.

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Q. The Gertig study that we've discussed today says that they have prospectively examined the relationship in a large cohort of U.S. women given the concerns for recall and selection bias.
Do you understand that?
MS. O'DELL: Objection to form.
A. I understand that.
Q. (BY MR. JAMES) So these studies are performed to address the flaws in the case control studies, correct?
MS. O'DELL: Object to the form.
A. They are a different type of study and they do account for recall bias, but they have their own weakness and limitations.
Q. (BY MR. JAMES) And we've already talked about today that, even in the Penninkilampi study that you've discussed in your report, they conclude with a note that prospective studies are warranted, correct?
MS. O'DELL: Object to the form; misrepresents the document.
A. They conclude with a note that prospective studies are warranted.
Q. (BY MR. JAMES) If we look back at the

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Langseth study.
MS. O'DELL: 19.
Q. (BY MR. JAMES) Did you locate it before I did?
A. I got it.
Q. Okay. I'm coming behind you here. You see on page 3 --
A. My -- it's not paginated, but I'm on the third page.
Q. Oh, thank you. And it's actually -- it should be on page 2 because there's only three pages.
A. Okay.
MS. O'DELL: Is there a specific place you want her to read?
MR. JAMES: I'm still looking. (Examined exhibit.)
Q. (BY MR. JAMES) Do you see in the bottom paragraph where the authors there call for the --
A. "Proposal; To Research Community?
Q. Yes. They call for the performance of prospective studies.
MS. O'DELL: Is there a specific place you're pointing her to?

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MR. JAMES: In that section.
A. I have read this three times, and I'm not seeing it. Proposal: To Research Community.
Q. (BY MR. JAMES) Huh.
A. Are you looking at the next page, the next to the last paragraph?
Q. Oh. Yes. Thank you.
A. Okay.
Q. Page 3.
A. Page --
Q. It's the second to the last paragraph.
A. I gotcha. "While it would not be reasonable"?
Q. Yes, Doctor.
A. Okay. Yes, I see that.
Q. Okay. Again, they're calling there for cohort studies, cohort prospective studies, correct?
MS. O'DELL: Object to the mischaracterization.
A. Correct.
Q. (BY MR. JAMES) And we know that after the Langseth 2008 paper, we did have additional cohort data published, correct?
A. The Gates follow-up, you mean?

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Q. We had the Gates 2010 paper, correct? The Houghton WHI 2014 paper, correct?
Can you verbally answer, please?
A. Yes. I'm sorry.
Q. And the Gonzalez 2016 prospective paper, correct?
A. Correct.
Q. On page 16, you also remark that "The cohort studies were not designed specifically to look at talcum powder."
Do you remember making that remark?
MS. O'DELL: Where are you?
MR. JAMES: On page 16 of Dr. Smith's report.
BY MS. O'DELL: Oh, 16.
Q. (BY MR. JAMES) It's the third par- -- third full paragraph down. "In my opinion" paragraph.
A. "In my opinion, meta-analysis is the most valid and reliable way to study an issue like ovarian cancer, which is relatively rare and requires a long study period to detect. The cohort studies were not designed specifically to look at talcum powder. Instead, the use of talcum powder is

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only one of many queries."
Q. And that's the question I'm asking you right now.
So there you make the remark that cohort studies were not designed specifically to look at talc.
Is that a criticism you have of the cohort studies?
MS. O'DELL: Objection to the -- object to the form; misstates what's in Dr. --
Go ahead, Doctor.
A. I don't find it particularly critical. I mean, that -- they're studying lots of things.
Q. (BY MR. JAMES) So you do not include a criticism against the cohort studies for the fact that talcum powder is only one of many queries?
A. That is not a criticism.
Q. You also make the claim, and if you continue on reading, Doctor, that there's a lack of power in the cohort studies?
A. Yes.
Q. Okay. And what is that based on?
(Deposition Exhibit 26 referenced.)
A. The numbers. "Power" is the numbers.

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Steven Narod, who is a medical oncologist and epidemiologist, suggests that in cohort studies the critical threshold for finding -- because of the rarity of ovarian cancer, the critical number base is 200,000.
Only did one cohort study, which is Gates, reach 200,000.
Houghton -- Houghton had 61,576 women.
Gonzalez had only 41,654 sisters.
Kind of tiny and underpowered or lack of power, and those are epidemiologic terms.
Q. Did you consider the statements in Berge about the power of the cohorts?
A. I'd have to look at Berge again to see what that was. I found it.
Where do you see that?
Q. If you look at the right column, the first full paragraph.
A. What page, please?
Q. Oh, thank you.
A. Oh, do you have a prob- --
Q. It's page --
A. Is this your bad problem?
Q. Yes. We're gonna --

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A. Which table does it have on it? Does it have Table 2 on it?
Q. Yeah. We're looking at page 6 --
A. Okay.
Q. -- of Table 2.
A. Table 2 page.
Q. Yes. Thanks, Doctor.
A. All right. Now, okay, so right-hand or left-hand column?
Q. It's the right-hand column.
A. Okay. Paragraph number?
Q. It's the first full paragraph --
A. Okay, great.
Q. -- in the right-hand column.
A. Got it.
Q. And are you reading that paragraph?
A. Yes.
Q. Thank you.
A. (Examined exhibit.) He's talking about heterogeneity. I don't think he's . . .
Q. So that -- Doctor, may I ask you a question?
A. Certainly.
Q. All right.

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So that paragraph concludes with the statement that, quote, "Low power of cohort studies cannot be invoked as explanation of the heterogeneity results," closed quote, correct?
A. I am -- I agree with you that that is what it says.
Q. Okay.
A. I cannot agree to that interpretation.
Q. Have you performed your own power calculations in this case?
A. I have not.
Q. Okay. Do you have any reason to disagree with the power calculations set forth in the Berge paper?
MS. O'DELL: Object to the form.
A. The data from the Narod paper.
Q. (BY MR. JAMES) Do you have any other basis upon which you would disagree with the Berge power calculations?
A. No.
Q. On page 16 of your report, you discuss a range by which you believe the risk of ovarian cancer is increased by way of talc use, and you conclude that it is a 20 to 50 percent range.

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Do you see where I am?
A. I know I wrote that, but -- yes, I found it.
Q. Super.
It's in the paragraph --
A. Right.
Q. -- above Mechanisms?
A. Right.
Q. Where do you get that range from?
A. Smith-Bindman. I don't think I -- I -- okay. So over all the studies, the meta-analyses, they ran from a 1.2 to a serous subtype 1.5.
In that range, it -- that would be a 50 -- 20 to 50 percent increase in ovarian cancer.
Q. In the course of answering that question, did you reference Smith-Bindman?
A. Yeah, at the time I wrote this report, I hadn't seen her individual analysis, so I couldn't have had that information when I wrote this. I have seen it subsequently.
Q. When you did look at that report?
A. Her deposition. Probably, I don't know, a week-and-a-half ago, week ago. The days are running together. Maybe as much as two weeks ago. I don't

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remember it in relation to Christmas.
MS. O'DELL: Do you remember -- do -- are you referring to her report?
A. Is that her report? Oh, yes, it's not her deposition. It's her report.
Q. (BY MR. JAMES) Did you look at any other expert reports in this litigation that we haven't discussed today?
A. I have seen Plunkett.
Q. Okay. Any others?
MS. O'DELL: Other than the ones we've talked about previously.
A. Crowley, Longo. None of the GYN oncologists. I can't think of any other.
Q. (BY MR. JAMES) Do you know why you were provided the Smith-Bindman report?
A. Can I tell you why I enjoyed it?
Q. No.
Do you know why you were provided it?
A. I suppose the lawyers wanted me to read it.
Q. Did you ask for it?
A. No.
Q. Did you ask for the report from

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Dr. Plunkett?
A. No.
Q. Those reports that you are provided in this case were selected for you by plaintiffs' counsel, correct?
MS. O'DELL: Object to the form.
A. Those two reports.
Q. (BY MR. JAMES) So to opine that there's a 20 to 50 percent increased risk for ovarian cancer by way of talc use, you said that you -- how did you get to the 50 percent again?
A. That was a high limit in serous in Gerrig --
Q. In Gertig?
A. -- Gertig. In Gertig.
The low range was 1 point. I think it's 22 or 21. So I put that range.
Q. And do you have any opinion about where the risk actually falls in that range?
MS. O'DELL: Object to the form.
A. Let's say it's 20 percent. Let's look at the lowest possible increase in risk. And let's look at the percentage of women who use talc.
We -- when you use various parameters

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such as Narod did, you're going to come up with hundreds of lives interrupted by ovarian cancer. So even a 20 percent increase is amazingly clinically significant and severe.
Q. (BY MR. JAMES) Dr. Smith, with due respect, that wasn't the question that I asked you.
A. Okay.
Q. My question to you is: You've cited in your report a range of a 20 to 50 percent increased risk of ovarian cancer, correct?
A. Yes.
Q. And my question is: Do you have an opinion about where -- a more precise opinion about where the risk actually falls in that range?
MS. O'DELL: Object -- object to the --
A. I --
MS. O'DELL: -- form. The report speaks for itself.
A. I think that range encompassed what the truth is. I don't know an exact number that I can give you.
Q. (BY MR. JAMES) And when you answered my question in discussion about the 20 percent

increased risk . . .
A. I was giving you the lowest number.
Q. And you answered my question -- in the manner that you answered my question, that's with the assumption that it is a real increased risk, correct?
MS. O'DELL: Object to the form.
A. Correct.
Q. (BY MR. JAMES) On page 16 and 17 of your report, you include a discussion of migration?
A. Yes.
Q. And you include the phrase that it is, quote, "universally accepted," close quote, by the gynecological community --
A. Correct.
Q. -- that "the female genital tract functions as a conduit for foreign material to enter the peritoneal cavity."
Do you see where I was reading?
A. I see exactly where it's reading.
Q. On what basis do you support your claim that it is universally accepted?
A. It's what we teach medical students and residents. We have the data of Egli and Sjösten

and -- starts with a K -- uterine peristalsis, and the Alba tubal transport dysfunction literature through infermil- -- infertility. Looking at nonflagellated particles that go through from the outside world to the peritoneal cancer -- peritoneal cavity via the vagina, cervix, uterus, fallopian tube, peritoneal cavity.
We certainly have all the bacteriologic information from chlamydia. Looking at the shot we have all the information -- consistent information on decreasing incidence of ovarian cancer with tubal ligation, with hysterectomy that blocks that open channel.
This is -- this is universally accepted in my gynecologic/obstetric population. I've seen it cited in the FDA without footnote. It's kind of like the sun's gonna rise tomorrow and things get from the outside world to the peritoneal cavity through the patent genital tract of a woman.
Q. Do you believe it's universally accepted that talc is one of the foreign materials that can migrate through the genital tract?
A. I believe it is. It's a particulate. It's in the range of all the particles that -- that

have gone from outside to inside.
Q. We've talked about the IARC today, correct?
A. Yes.
Q. Do you know that the IARC has called the evidence concerning migration to be relatively weak?
A. May I see that statement?
Q. I'm asking you if you're familiar with it?
A. I don't remember that statement.
Q. You referenced the FDA statement on migration.
What are you referring to there?
A. I think they say it's something like universally accepted or everybody acknowledges. I don't remember the exact words, but they -- they say that it's what happens.
Q. Do you know if the FDA statement you're referring to pertains specifically to talc?
A. No, it doesn't particularly -- it -- it . . .
MS. O'DELL: If you need to see the statement again, Doctor --
THE WITNESS: Okay. It should --
BY MS. O'DELL: -- please take a look.

THE WITNESS: -- be on the bottom down here.
You want to pull IARC while you're there?
I know it's here. It's one of the early, early -- nope. We're getting there.
BY MS. O'DELL: Here you go.
THE WITNESS: We're getting close to it.
BY MS. O'DELL: (Inaudible.)
THE WITNESS: I got it. And that's -- that's the petition. Here's the FDA.
BY MS. O'DELL: No, no. That's --
Q. (BY MR. JAMES) Here, I'll see if I can find somewhere.
A. 8?
Q. Did we find the FDA letter?
MS. O'DELL: Exhibit 8.
MR. JAMES: Okay. Super.
A. (Examined exhibit.) I am not finding what I'm looking for.
Q. (BY MR. JAMES) You want to look on page 5 of the letter, Dr. Smith? I think that's where you're looking.

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A. Oh, okay.
Q. And it's the third full paragraph down.
A. Here we go. Here we go.
(Examined exhibit.) Right. "The potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable."
Q. So that statement is not a direct statement about talc, correct?
A. Correct.
MS. O'DELL: Object to the form.
Q. (BY MR. JAMES) You say in the section of your report that you reviewed the small number of articles that dispute talcum powder's ability to reach the tubes and ovaries, but that you, quote, "rejected those claims."
Do you see that passage of your report?
A. Yes.
Q. What studies did you review and reject?
A. The one with the cynomolgus monkeys -- I can't say that right, cynologus monkeys. I know the name of the author.
Q. Are there any other studies that --

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A. There's two of them.
Q. Sorry, Doctor.
A. I'm sorry. There's one with -- there's one with two monkeys, and there's one with six monkeys or five monkeys, about like that.
Anyhow, they didn't -- they put particulate in the vagina. It did not transport into the peritoneal cavity of these sacrifice monkeys. And I apologize for spacing out on the name of the author. Um --
Q. Are -- sorry, Doctor.
MS. O'DELL: Yes, go ahead. Sorry.
A. There's a rodent study by Wiener, Weiner that did not get -- well, everything went through, including the controls for black carbon and then nothing went through. Let me think of the author of those monkeys. Nothing went through in the next set of experiments.
The absence of evidence is not evidence of absence. The fact that it doesn't go through in somebody's study is not as significant as it does go through in somebody else's.
Q. (BY MR. JAMES) In somebody else's study?
A. Right. Like even the Sjösten person with

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talc -- I mean, not talc -- corn starch on gloves, seeing those pelvic exam under anesthesia and then looking for starch in the peritoneum when the ladies get a subsequent hysterectomy, some of the patients did not have starch particles go through, but the majority did. So it doesn't have to go through every time to prove a point.
Q. Do you believe you conducted a comprehensive review of the literature relevant to the issue of migration?
A. I do.
Q. Did you review all of the relevant animal studies pertaining to the issue of migration?
A. I tried to. I know more about rat and rabbit ovaries than I want to.
MS. O'DELL: There's no question pending, Doctor. Thank you.
Q. (BY MR. JAMES) You discussed the tubal ligation data earlier --
A. Yes.
Q. -- correct?
A. Yes.
Q. Okay. What is your view on the tubal ligation data? Do you find the data there

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consistent or inconsistent?
MS. O'DELL: Object to the form.
A. I find it consistent.
MS. O'DELL: Excuse me. Sorry. Keep going.
Q. (BY MR. JAMES) And earlier today, we discussed the Terry 2013 study, correct?
A. Yes.
Q. Okay. Do you know what the Terry study had to say about the tu- -- tubal ligation hypothesis?
A. Not without looking at it. Uh-oh. I've got that bad copy that's missing part of a page.
Q. That's a different copy, Doctor.
A. That's Katherine Terry.
Q. Oh, is it?
A. The first study. It's got a badly copied page, so we had to go to the originals. I don't know if it's on that page, but . . .
MS. O'DELL: I've got it here.
A. Oh, here. I found the -- the tubal ligation paper -- chart is on a different page. It's not the bad page.
Q. (BY MR. JAMES) And are you looking at

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page 819, Doctor?
A. Yes.
Q. Okay.
A. This has in the cases with ovarian cancer there was a lower incidence of tubal ligation than in the controls in this study.
Q. You'd agree the data of the Terry paper is not supportive of the tubal ligation hypothesis, correct?
MS. O'DELL: Objection; form.
A. In this study, the cases had a lower instance of ligation than the patients with ovarian cancer. So this is not a data point in the whole literature of tubal ligation and its protective effects.
Q. (BY MR. JAMES) Did you discuss this finding of the Terry paper in your report?
A. I don't think I did.
Q. Why not?
A. Because I think I made a -- a very broad statement about tubal ligation.
Do you know exactly where that is?
Q. Are we looking at the report or the paper, Doctor?

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A. I'm looking at the report on tubal ligation.
MS. O'DELL: I think you're looking for page 3, Doctor.
THE WITNESS: About what?
MS. O'DELL: Page 3.
THE WITNESS: Back to page 3?
A. Oh, the risk? There it is. "Additionally there are factors that are recognized as protective that include tubal ligation, oral contraceptive use, salpingectomy, salpingo-oophorectomy, hysterectomy, and breastfeeding."
Yes, I did not cite the Terry study.
Q. (BY MR. JAMES) And then on page 14 of your report is where you include a more detailed discussion of Terry, correct?
A. Yes.
Q. Do you include any discussion there of the tubal ligation data in that setting?
A. I do not.
Q. In fact, you do say here that -- just for all candor here, Doctor, if we look on page 14 of your paper, you say that "There was no association with parity, OC use, tubal ligation status, or

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menopausal status."
Do you see where I'm reading? I'm on page 14 of your report.
A. I don't think -- I think it came out to be not statistically significant.
Q. Correct.
So you do have this report in here, correct?
A. Yeah.
Q. Okay. So the data, according to your report on tubal ligation, is inconsistent, isn't it?
MS. O'DELL: Object to the form.
A. This single study does not support my earlier station. But again, the totality of the literature on tubal ligation supports it as decreasing risk factor for ovarian carcinoma and even your -- some of the other things cited tubal ligation.
MS. O'DELL: What are you looking for, Doctor?
THE WITNESS: SGO and the PDQ risk factors.
MS. O'DELL: Uh-huh.
THE WITNESS: Yeah.

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A. "If a patient has her tubes tied, a tubal ligation, her risk is deeply reduced."
"Tubal ligation benefits based on solid evidence, tubal ligation is associated with a decreased risk of ovarian cancer."
Q. (BY MR. JAMES) Do you find those SGO and ACOG statements that you just referred to to be informative about risk factors for ovarian cancer?
MS. O'DELL: Object to the form.
A. No. What I found to be informative of my assessment of tubal ligation is a comprehensive view of all the literature on tubal ligation through numerous papers and a full report that ultimately was cut out of this in one of my reports in the early drafts.
MS. O'DELL: Don't discuss drafts.
THE WITNESS: I'm sorry.
MS. O'DELL: Thank you.
THE WITNESS: I'm sorry. I dropped it again.
A. I have completely reviewed the literature. I know all the literature on tubal ligation. You have -- I mentioned earlier the -- the Cramer study that shows tubal ligation increased ovarian cancer;

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whereas, Terry's not statistically significant, but that's beta error, finding difference where none exist.
The -- the totality of the literature, not just a couple of funky websites, tell me that tubal ligation decreases the incidence of ovarian cancer, and that is because it interrupts the conduit from the outer world to the peritoneal cavity.
Q. (BY MR. JAMES) Do you have the Terry paper in front of you still, Dr. Smith?
A. Yes.
Q. Okay. If we look at page 819, in the right-hand column, the bottom first --
MS. O'DELL: Excuse me, Scott. Can you give me just a minute to get there? I can't find it.
MR. JAMES: Sure.
MS. O'DELL: Yeah. Thank you.
What page?
MR. JAMES: 819, the bottom first full paragraph that leads with the words, "The biological plausibility."
A. Um-hum. I'm there.

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Q. (BY MR. JAMES) Do you see where I am?
A. Yes, I am.
Q. Okay. If you drop down about halfway through that paragraph --
A. Uh-huh.
Q. -- the article states, quote, "Talc-containing powders are hypothesized to promote cancer development by ascending the female genital tract and interacting directly with the ovarian surface epithelium leading to local inflammation."
A. Correct.
Q. Do you agree with the Terry characterization of that?
MS. O'DELL: Would you mind reading the full sentence, please?
A. "Talc" --
MS. O'DELL: Excuse me. Not you.
THE WITNESS: Oh, sorry.
MR. JAMES: Sure. Where did I leave off, Leigh?
MS. O'DELL: You left off "leading to local inflammation," and then you stopped.
Q. (BY MR. JAMES) Okay. "Characterized by increased rates of cell division, DNA repair,

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oxidative stress, and elevated and inflammatory cytokines."
Do you see that per- -- that sentence that I read?
A. I do.
Q. Okay.
A. Yes.
Q. Do you agree with the Terry authors that that is a hypothesis?
MS. O'DELL: Objection to form.
A. Yes. I think at the time this was written . . .
Yes, I think that is a hypothesis that many people have drawn and is drawn in this paper.
Q. (BY MR. JAMES) Dr. Smith, with respect to your report section that discusses NSAIDs. So I'm moving on.
A. Yes.
MS. O'DELL: Hey, Scott, if you're moving on to another topic, can we take a short break?
MR. JAMES: Absolutely.
MS. O'DELL: Thank you.
THE VIDEOGRAPHER: Going off the

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record. The time is 5:17 p m.
(A recess was taken from 5:17 p m. to 5:37 p m.)
THE VIDEOGRAPHER: This marks the beginning of Disk 3 -- excuse me, Disk 4. Back on the record. The time is 5:37 p.m.
Q. (BY MR. JAMES) Dr. Smith, are you aware that the cohort studies that we've discussed today have also considered the migration hypothesis by considering the data on tubal ligation and ovarian cancer?
MS. O'DELL: Object to the form.
A. I need to look at those studies for the specific information. May I retrieve them?
Q. (BY MR. JAMES) Sure. If I --
A. Nope.
Q. If I can refer you first to the Houghton WHI study.
A. Sure. Okay, Gates.
I need Gertig and I -- have you given me Gonzalez?
Q. We have not marked Gonzalez.
A. Okay. Then I will not look for it.
(Examined exhibit.) Yes.

Q. Okay. So are you aware that the cohorts also included data on that hypothesis?
MS. O'DELL: Object to the form.
A. Now I am, yes.
Q. (BY MR. JAMES) Did you cite that data in your report?
A. I did not.
Q. Earlier you discussed that in acknowledging the Terry finding on tubal ligation that you had considered the entire body of literature, correct?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) And that's one of the reasons that you discounted the Terry finding on the tubal ligation migration issue, correct?
MS. O'DELL: Object to the form.
A. I didn't discount it. I think the preponderance of all the literature on tubal ligation overpowers a single or two or three reports that do not find tubal ligation important, either not statistically significant or impair prognosis -- increase risk of ovarian cancer.
Q. (BY MR. JAMES) Would you weigh the cohort

data on this issue more heavily than the case controlled data on this issue?
MS. O'DELL: Object to the form.
A. No.
Q. (BY MR. JAMES) Would you consider the data on equal footing?
MS. O'DELL: Object to the form.
A. I con- -- I can consider all of these individual studies equally.
Yes. I consider the case control if -- just because it's a case control study about effects of tubal ligation compared to a cohort study, I don't think that weight is about pa- -- recall of tubal ligation.
There -- there are studies on women recalling whether they've had a surgical procedure to end their fertility and they're pretty accurate because it's pretty important to every woman.
Q. (BY MR. JAMES) Are you aware of any prospective cohort data that supports the tubal ligation migration hypothesis?
MS. O'DELL: Object to the form.
A. I cannot give you one off the top of my head.

Q. (BY MR. JAMES) And you didn't discuss any of that data in your report, correct?
A. I did not.
Q. Discussing now where we left off, Dr. Smith, the data on NSAIDs.
A. Yes.
Q. In your report, you acknowledge the literature on NSAIDs and ovarian cancer risk as inconsistent, correct?
A. Yes. And in its totality.
Q. And earlier in your report when you list what you considered to be generally accepted protective factors, you do not list NSAIDs, correct?
A. Correct.
Q. Is that because you believe that it's not generally accepted that NSAIDs apply a protective effect for ovarian cancer?
MS. O'DELL: Object to form.
A. I don't think we have found the right anti-inflammatories because I don't think we, as a scientific community, do not understand the critical points in inflammation and carcinogenesis and disease progression.
So I believe in the future -- and I

think this is critical -- in the future in laboratory studies when we discern the actual mechanisms of carcinogenesis, enzyme changes, reactive oxygen species, DNA damage, aneuploidy, malignancy, that we will be able to affect inflammation and interrupt it in a -- in a very progressive, protective way. I think that's coming, and it's gonna come out of the lab.
Q. (BY MR. JAMES) Is it fair to say that we're not there yet?
A. We're not there yet.
Q. Are you aware, as of today, with doctors -- a doctor following a standard of care to prescribe NSAIDs to decrease ovarian cancer risk?
A. Not in ovarian cancer.
Q. Would you agree that some types of inflammation don't increase cancer risk?
MS. O'DELL: Object to the form.
A. I can think of examples of an acute single inflammation episode that's been studied and not had long-term cancer effects, but I think what we know about cancer is that it is chronic inflammation, repeated insult, the snowballing of the inflammatory cascade inducing enzyme, changes reactive oxygen

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species, reactive nitrogen species and ultimately DNA alteration, inducing driver mutations and starting this thing going and then causing it to progress.
Q. (BY MR. JAMES) Do you believe rheumatoid arthritis is associated with cancer?
A. I have not reviewed that literature, and I cannot comment on that.
Q. Can you think of any inflammatory conditions, as you sit here today, that are not associated with cancer?
A. That are not associated with cancer?
Q. Correct. Correct.
MS. O'DELL: Object to the form.
A. I haven't studied all inflammatory conditions.
Q. (BY MR. JAMES) Did you look for genotoxicity studies in conducting your review in this case?
A. Yes.
Q. Okay. Did you review any?
A. Yes.
Q. Which ones?
A. There is an article on nanoparticles and

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talc. There is -- and I cannot remember the name of the author for the life of me. I can see the heading and there is a growing body of evidence on the role inflammation plays in the development of ovarian cancer.
And their initial papers are more about oxidative stress in the pathogenesis of ovarian cancer. A group at Wayne State University have been looking at this for several years.
Q. Do you know Dr. Saed?
A. I have never met him. I've just read his stuff.
Q. Had you read his papers before you were retained as an expert in this litigation?
A. Yes.
Q. You had read his papers?
A. Yes.
Q. When did you read his papers?
A. Just in the course of -- he's presented at SGO before.
Q. Do you know when?
A. I know he -- oh, I know he had an abstract in '17. I think he's been there before that. And then I went deep diving into his paper after I was

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asked to review his literature.
Q. Do you know anything about his connection to this litigation?
A. Yes, I do.
Q. What do you know?
A. I know that I suggested to Dr. Thompson that she get in touch with him and start reading his literature.
Q. So were you the first point of contact between plaintiffs' counsel and Dr. Saed?
A. I was the name. I was the person that gave them his name.
Q. And how did you know Dr. Saed again?
A. I don't know him. I just read his papers.
Q. How did you become --
A. I think they're good.
Q. How did you become familiar with him or aware of him, just through his papers?
A. Through his papers and looking at inflammation in ovarian cancer and reading GY -- he's published in GY Oncology before. I just knew his paper. Maura Fletcher [sic, Nicole] who's in his lab, I think I saw her papers first.
Q. Do you know Fletcher?

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A. I don't know any of them. I don't know anybody in -- I don't know where Wayne State is. It's in Michigan somewhere. I don't know anybody there.
Q. Do you know if plaintiffs' counsel had a litigation relationship with Dr. Saed before you identified Dr. Saed as someone they should contact?
A. I don't know if they did, but they may have. I don't know that.
Q. Do you know anything about the funding of his studies?
A. I do not.
Q. And when were you retained in this litigation, it was 2017?
A. January of 2017 was the first time that they asked me to look at the literature.
Q. I looked at your references in your materials considered list. I didn't see reference to an Endo-Capron study.
Does that title ring any bells with you, Endo-Capron?
A. I don't -- it does not ring any bells.
Q. If that study and a body of other studies on genotoxicity are not listed in your references

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list or your materials considered list, may I assume, then, that you didn't review those studies?

MS. O'DELL: Excuse me. I object to the question. I think it's vague. If there's a specific study you want to ask her about, then you know she's happy to review it and comment if you ask her questions, but to the degree you've referenced, quote, "a body of literature," that may not be the way Dr. Smith is aware of it.

I object to the question.

MR. JAMES: Speaking objection is noted. You can answer the question.

MS. O'DELL: Objection is noted.

MR. JAMES: Your speaking objection is noted. That you've been speaking all day. So thank you.

A. Could you ask the question again? I'm so lost.

Q. (BY MR. JAMES) Okay. Let's start with the Endo-Capron study.

If the Endo-Capron study is not listed in your materials considered or reference list, then may I safely presume that you did not review that study?

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MS. O'DELL: Objection. It goes to --

A. Do you know who the author is?

MS. O'DELL: Excuse me. Excuse me. Object to the form.

A. I mean, do I know -- would I know it by an authors' name or another name of Endo-Capron?

Does it stand for something?

Q. (BY MR. JAMES) If you have not listed the study in your references or materials considered list, then may I assume or presume that you did not review that study?

MS. O'DELL: Object to the form.

A. I don't recognize that study. I -- with -- I can't give you more information.

MS. O'DELL: It's --

Q. (BY MR. JAMES) If you have reviewed --

MR. JAMES: This is a very simple question, Leigh.

Q. (BY MR. JAMES) If you have reviewed a piece of literature, whether you've cited it, considered it, or referred to it, it would be listed somewhere in your references list or your materials considered list, correct?

MS. O'DELL: Objection to form.

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A. I would presume so.

Q. (BY MR. JAMES) Are you aware of any studies that have reported inflammation, granulomas, or foreign body reactions in the ovarian tissue of a woman following her usage of talcum powder products?

MS. O'DELL: Object- --

A. I --

THE WITNESS: Sorry, were you saying something?

MS. O'DELL: Give me just a moment here.

A. I know of -- I do not know of a human study with talc related granuloma.

Q. (BY MR. JAMES) With respect to your Bradford Hill analysis, Dr. Smith, we have covered a lot of that along the way today, and so I'm going to jump around just a little bit in hopes of moving us along. Okay?

A. Okay.

Q. So with regard to specificity, which is one of the factors you've analyzed in your report, correct?

A. Yes.

Q. Do you believe that factor was met here on

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this body of literature?

A. I . . . I think the --

Q. And I believe -- sorry, Doctor.

A. -- body of all the work cited here supports that criteria. I don't think that's as important as the consistency and the strength.

Q. We have discussed strength earlier today, and I don't want to replow ground that we have plowed, but, in your opinion, is the criteria of strength met on this body of literature?

A. I believe that.

Q. Can you cite any study or scientific literature that characterizes the association at issue as an association that is strong?

MS. O'DELL: Object to the form.

A. The numbers are what they are and statistically significant and clinically significant.

Q. (BY MR. JAMES) Can you cite to a single study that characterizes the odds ratio or association as strong?

MS. O'DELL: Object to the form.

Q. (BY MR. JAMES) That's a "yes" or "no" question.

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MS. O'DELL: Object to the form.
A. I haven't read the word "strong" in those studies.
Q. (BY MR. JAMES) Do you believe the criteria consistency is met?
A. Oh, yes.
Q. Do you acknowledge that there is an inconsistency with respect to the results based upon the design study -- correct?
MS. O'DELL: Objection to the form.
A. You mean the cohort studies?
Q. (BY MR. JAMES) Yes. Do you acknowledge that there is an inconsistency between the results produced by the cohort studies as compared to the results produced by the case control studies?
A. Individually, but not in the meta -- not with their inclusion in the meta-analyses.
So you're looking at individual studies, but when they go into the whole stew pot it becomes statistically significant and consistent.
Q. And that brings us back to the word of heterogeneity that we discussed a bit earlier in the Berge study.
But do you understand that in the

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Berge study one of the detractors from the causal interpretation was the heterogeneity between study and design?
Do you understand that?
MS. O'DELL: Object to the form.
A. They didn't quantitate heterogeneity like they did in the Penninkilampi study which actually quantitated heterogeneity on the Newhouse Ottawa Scale [sic, Newcastle], so I think it's better to look at that. And none -- none of the studies in Penninkilampi had an NOS score less than 5, which meant they didn't have to get rid of anything for lack of -- for -- because of heterogeneity, and the cohort studies were in there. So I think we have a better idea of assessment of heterogeneity in that -- in that study.
Q. (BY MR. JAMES) Okay. And my question is: Do you acknowledge that in the Berge study, one of the reasons the authors of that study concluded that the caus- -- causal interpretation was not appropriate was because of the lack of consistency between study design?
MS. O'DELL: Object to form.
A. I agree with you that is a quote from that

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study.
Q. (BY MR. JAMES) We discussed already that in the Penninkilampi study the finding that they included in that study based upon cohort studies omitted the data from the Gates 2010 study, correct?
MS. O'DELL: Object to the form.
A. Correct. We have discussed that.
Q. (BY MR. JAMES) Would you agree that a lack of data on dose response, in a hypothetical situation, would counter against a causal interpretation?
MS. O'DELL: Object to the form.
A. That is one of the factors that one considers in determining causality.
Q. (BY MR. JAMES) Do you believe dose response is met on the body of literature here?
A. On the epidemiologic da- -- data, it -- their dose response is equivocal. Penninkilampi found dose response in the -- in the meta-analysis, whereas Berge didn't.
Q. Let me finish, Doctor. I'm sorry.
A. I think it's -- as I said in my report, it is very difficult, even if you look at -- so many studies did not look at frequency and duration.

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For example, Gertig, one of the cohort studies is ever/never in 1982. But many of the other studies didn't look at dose, duration, frequency, and how do you -- how do you establish dose in pouring powder on your bottom.
So I -- I am not surprised that it's been in the epidemiologic literature very difficult to establish clear dose response curves.
Q. You mentioned the Gertig study in your answer, Dr. Smith.
And do you understand that the Gertig study did look at frequency?
A. I thought the Gertig study was the Nurses' study, and they asked in 1982 ever/never, single time, and they never queried again.
Q. So you're unaware of the fact that the Nurses' Health study included information on frequency?
MS. O'DELL: Objection; form. Misstates.
A. Let me look at it. It's right on top.
(Examined exhibit.) They were given one assessment, no daily, one to six times a week, less than once a week, on sanitary napkins, yes, no,

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one time.
That's not -- that's not a decent frequency and duration. I'm sorry. You don't know how long. You ask it one time. You don't account for changes in practices. That's not valid.
Q. (BY MR. JAMES) Do you acknowledge that frequency is a valid measure of dose response?
MS. O'DELL: Object to the form.
A. It's a measure of assessing dose response.
Q. (BY MR. JAMES) Do you acknowledge duration is a measure of assessing dose response?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) Are you aware that there are case control studies that have looked at duration and frequency and found no dose response?
MS. O'DELL: Object to the form.
A. Yes.
Q. (BY MR. JAMES) And, in fact, the studies that -- those studies are cited in your Exhibit B, correct?
A. These are only single case control studies in Exhibit B, and I looked at dose responses. I read through the studies, and they attempted to do

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that.
Q. You acknowledged that some of the dose -- excuse me, some of the case control studies that you cited do not show dose response, correct?
A. I would say the majority do not show dose response with a single epi case control studies.
Q. Did you consider the findings in the studies that you cited and in other literature pertaining to the use of talcum powder on condoms, diaphragms, or sanitary napkins?
A. No.
Q. Why not?
A. Well, the good people that make condoms eliminated talc exposure on condoms in the 1990s. That's a very smart move.
And then you start breaking down sales of these populations into small enough groups that you lose the ability to have statistical significance.
Q. Do you understand the number of articles that you've cited and discussed in your report do include -- include finding on odds ratios associated with sanitary napkins, diaphragms, and condoms?
A. Right. And I -- and I put some of those

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on my Exhibit B chart in the Comments section.
Q. And so my question that I think I originally posed is: Do you consider those findings relevant to your opinions today?
A. They are a component of my -- of genital talc use, so, yes, they are a component of my opinion.
Q. Do you understand the data in those studies does not show an association between the use of talcum powder on condoms, diaphragms, and sanitary napkins in ovarian cancer?
MS. O'DELL: Object to the form.
A. Most -- most studies, when you broke them down, they lost -- they did not have statistical significance. Your statement is correct.
(Discussion off the record.)
MR. SILVER: Could we go off the record?
THE VIDEOGRAPHER: Going off the record. The time is 6:05 p m.
(A recess was taken from 6:05 p m. to 6:16 p m.)
THE VIDEOGRAPHER: Back on the record. The time is 6:16 p m.

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MR. JAMES: Dr. Smith, thank you for your time. That's all the questions I have for now.
THE WITNESS: Thank you.
EXAMINATION
BY MR. KLATT:
Q. Dr. Smith, my name is Mike Klatt --
A. Hi.
Q. -- and I represent Imerys Talc America.
Do you know what Imerys Talc America is?
A. Yes.
Q. What are they?
A. They are -- own the mines from which the talc is mined.
Q. Do you know what years they owned the mines from which the talc is mined and used in the Johnson & Johnson talc-based body powder product?
A. I know it's more recent, but I don't know the exact dates.
Q. Do you know who owned the mines before Imerys owned them?
A. Lusignac, which I think was J&J.
Q. No, Lusignac is Imerys, my client.
A. Oh, is Imerys. Okay.

Q. So who owned it before Lusignac and Imerys? Do you know?
A. J&J, I believe.
Q. Okay. I'm gonna skip around because a lot of ground's been covered today --
A. Okay.
Q. -- and I just have follow-ups on a bunch of different areas, so --
A. Okay.
Q. -- I'll be skipping from subject to subject, and it's pretty random here.
You said earlier today that you knew Dr. Hal Lawrence with ACOG?
A. Yes.
Q. If you communicate with Dr. Hal Lawrence, or anybody else outside of this litigation, on the subject of talc and ovarian cancer, are you gonna disclose to them that you're a paid expert for plaintiffs in the litigation?
BY MS. O'DELL: Object to the --
A. No.
MS. O'DELL: Object to the form.
A. No. And I haven't talked to Dr. Lough- -- Lawrence in 40 years.

Q. (BY MR. KLATT) Okay. But I'm just asking in the future.
Q. (BY MR. KLATT) You understand that Imerys tests talc of competitors. It tests talc from mines that are never used for body powder. It tests talc from portions of mines that are never used for any purpose.
You can't tell me that any of these samples ended up in Johnson & Johnson Body Powder, can you?
MS. O'DELL: Objection to the form; misstates the evidence, misleading, mischaracterizes the document.
A. (Examined document.) 9-9-1975, Johnson's Baby Powder anthophyllite and tremolite on the 28.
Q. (BY MR. KLATT) And do you have any proof that Imerys owned the mines that that sample came from at the time it was tested?
MS. O'DELL: Objection.
A. I don't.
Q. (BY MR. KLATT) I'm sorry?
MS. O'DELL: Objection.
A. I don't know when Imerys bought the mine.
Q. (BY MR. KLATT) And let's mark what you're

looking at as the next exhibit, 28. If you can please, Dr. Smith, put this sticker on here.
(Deposition Exhibit 27 and 28 marked for identification.)
Q. (BY MR. KLATT) Have you read Dr. Hopkins multiday deposition where he was questioned about what you're looking at right now, Exhibit 28?
A. I have not read it in detail.
Q. Have you read Ms. Pier's deposition where she was questioned about Exhibit 27?
A. I have not read it in detail.
Q. Do you know that Exhibit 27 and 28 that you're looking at are attorney created charts?
MS. O'DELL: Objection; misrepresents the record.
MR. KLATT: Not at all. It's exactly what happened.
MS. O'DELL: Objection.
A. I have another J&J sample here from 3-3-87. You want to just --
MR. JAMES: Objection; nonresponsive.
Q. (BY MR. KLATT) Have you read Dr. Hopkins multiday deposition that resulted in the creation of Exhibit 28 --

(Speaking simultaneously.)
A. No.
Q. (BY MR. KLATT) -- or Ms. --
A. Not in detail --
Q. -- or Ms. Pier's --
A. -- no.
Q. -- deposition --
MS. O'DELL: Let him finish.
Q. (BY MR. KLATT) -- that resulted in the creation of Exhibit 27 to your deposition?
A. Not in detail.
Q. Do you understand that they had explanations why each of those items that you're looking at had nothing to do with any asbestos in Johnson & Johnson Baby Powder?
MS. O'DELL: Objection.
A. I did not know that.
Q. (BY MR. KLATT) And if you were being objective, you would weigh their explanations in contrast to Dr. Longo's testimony that you're just accepting at face value, correct?
MS. O'DELL: Objection; misstates the record.
A. I think there are three different

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determinations.
Q. (BY MR. KLATT) Well, you're just assuming what Dr. Longo found was valid, correct?
MS. O'DELL: Objection. An expert is allowed to rely on another expert.
You may answer the question if you understand.
THE WITNESS: An expert is allowed to what?
MS. O'DELL: To rely on the findings of another expert as counsel knows.
A. I have no reason to doubt Dr. Longo's technique.
Q. (BY MR. KLATT) Do you know anything about his technique?
A. I have read it in his report, but I don't remember off the top of my head.
Q. Have you -- do you have any expertise yourself in how to test a product to see whether there's asbestos in it?
A. Only in the broadest general TEM, SEM, XRD case. I don't know how to perform any of those.
Q. But let's -- you would agree with me that you accept -- you don't know Dr. Longo

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personally, correct?
A. Not at all.
Q. And you know nothing about his background or qualifications, correct?
A. I have not --
MS. O'DELL: Objection.
A. -- studied his CV.
Q. (BY MR. KLATT) But you were willing to accept his conclusions about asbestos being in body powder at face value, but you didn't even bother to look at the explanations that Dr. Hopkins from Johnson & Johnson or Ms. Pier from Imerys gave that asbestos isn't in body powder --
MS. O'DELL: Objection --
Q. (BY MR. KLATT) -- correct?
MS. O'DELL: Objection to the form. Misstates the record.
A. I have not read their depositions.
Q. (BY MR. KLATT) If this court were to determine when it examines the evidence that Dr. Longo's testing does not show asbestos in Johnson & Johnson Body Powder, you would have no basis -- other basis to say that there is asbestos in Johnson & Johnson --

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MS. O'DELL: Objection. Incomplete --
Q. (BY MR. KLATT) -- body powders, correct?
MS. O'DELL: Excuse me. Objection; incomplete hypothetical. The Court will not make findings of fact. That's a jury's job and counsel knows that.
MR. KLATT: Absolutely not. This court can exclude that evidence under Daubert, and you know it.
MS. O'DELL: That's not a finding of fact, and you know that. End of story.
MR. KLATT: But they can find that the methodology used is inadequate to show that there's asbestos in this product.
MS. O'DELL: Which is not what you just said, and you know that, so it misstates the process.
(Speaking simultaneously.)
MR. JAMES: Ms. O'Dell --
Q. (BY MR. KLATT) Well, let me ask you this --
MR. JAMES: -- make your objections and let the record proceed.
Q. (BY MR. KLATT) If the judge in this

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case --
MS. O'DELL: The record --
MR. JAMES: That's the way it's supposed to work.
Q. (BY MR. KLATT) If the judge in this case concludes that Dr. Longo's methodology is inadequate to show that asbestos is in Johnson & Johnson Body Powder, then you have no basis to say that it is, correct?
MS. O'DELL: Objection to the form. Misstates the record.
A. I'd have to think about that.
Q. (BY MR. KLATT) Are Exhibit 27 and 28 and Dr. Longo's testing the only documents you're relying on regarding asbestos being in Johnson & Johnson Body Powder products?
MS. O'DELL: Objection to form.
A. No. There is the Blount deposition that --
Q. (BY MR. KLATT) Do you know whether that has anything to --
MS. O'DELL: Let her finish, please, sir.
Q. (BY MR. KLATT) I'm sorry. Go ahead.

MS. O'DELL: Let her finish.
Go ahead.
A. -- that identified asbestos in Baby Powder, Johnson's -- the -- that she identified as Johnson's Baby Powder.
Q. (BY MR. KLATT) Do you know whether that Baby Powder --
MS. O'DELL: Let her -- I don't think she's done.
Q. (BY MR. KLATT) -- was supplied by Imerys?
MS. O'DELL: I don't think she -- she's done.
A. I haven't finished thinking. I cannot think of another example at the top of -- off my head at this hour.
Q. (BY MR. KLATT) Do you know whether Dr. Blount's finding of asbestos that you just referred to involved talc supplied by Imerys?
A. As I answered previously, I do not know when Imerys assumed ownership of those mines.
Q. So you can't tell the Court whether Dr. Blount's testing was testing talc from Imerys or not, correct?
MS. O'DELL: Objection to form.

A. I cannot.
MS. O'DELL: Misstates the record.
Q. (BY MR. KLATT) You're charging $600 an hour; is that correct?
A. I am.
Q. Is that for all work you're doing in the case, including testimony, whether it's in a deposition or in a court of law?
A. I believe there's a flat daily rate. I'm not sure about this, but I believe that a flat daily rate of 800 hours in one day is only $5,000. That was an exaggeration. I'm trying to show that I've retained my sense of humor.
Q. I think what you were saying is that if testimony lasted all day there would be a flat rate of $5,000 --
A. Correct.
Q. -- is that correct?
But if it's broken down by an hourly basis, whether you're doing reading or testifying, it's all $600 an hour?
A. That -- I agree with that.
Q. Okay.
MR. KLATT: Can we go off the record

for a second. I think I'm done. I just need to look back over my notes.
THE VIDEOGRAPHER: Going off the record. The time is 7:06 p m.
(Ms. Brown left the room.)
(A recess was taken from 7:06 p m. to 7:39 p m.)
THE VIDEOGRAPHER: Back on the record. The time is 7:39 p m.
MR. KLATT: I'm done with my questioning, subject to any follow-up, so . . .
EXAMINATION
BY MS. O'DELL:
Q. Dr. Smith, I've got a few questions for you.
A. Okey-doke.
Q. I know it's been a long day so I'll be brief.
You were asked a series of questions about the presence of asbestos in Johnson's Baby Powder and Shower to Shower.
Do you remember those questions?
A. I remember I was asked them.
Q. Good answer to not a very specific

question.
Don't remember the specific questions, but you were asked about those topics?
A. Yes.
Q. And let me show you what I'm marking as Exhibit 29, which is Dr. Longo's report.
(Deposition Exhibit 29 marked for identification.)
Q. (BY MS. O'DELL) Are you, in part, relying on Dr. Longo's testing and his findings of the presence of asbestos in historical samples of Johnson's Baby Powder and Shower to Shower?
A. Yes.
Q. And from your review of Dr. Longo's report, he found -- did he find asbestos in a number of samples?
A. He found --
MR. JAMES: Objection; leading.
A. He found asbestos in 66 percent of the samples he tested.
Q. (BY MS. O'DELL) And did he test samples from a time period of the 1960s into the 1990s?
MR. JAMES: Objection; leading.
MR. KLATT: Object to form.

A. Yes. And memory serves the last date on his report was 2000, but there was a chart that I saw.
Q. (BY MS. O'DELL) Is -- is -- what other -- and you would defer to Dr. Longo on the testing methodology that's appropriate for identifying asbestos in Johnson's Baby Powder and Shower to Shower?
MR. JAMES: Objection; form.
A. Yes.
Q. (BY MS. O'DELL) Would you also -- well, strike that.
Did Dr. Longo also test for the presence of fibrous talc?
A. He did.
MR. JAMES: Objection; form.
Q. (BY MS. O'DELL) Did he -- were there -- what do you recall about Dr. Longo's findings regarding fibrous talc?
A. I believe the vast majority of his samples had fibrous talc. If memory serves, there's only one sample in which he could not demonstrate fibrous talc.
Q. And -- and you -- would you defer to

Dr. Longo on the methodology that's appropriate for testing Johnson's Baby Powder and Shower to Shower for the presence of fibrous talc?
MR. JAMES: Object to the form.
A. I would.
Q. (BY MS. O'DELL) Is there other evidence that you relied on in considering the question of -- of whether there is asbestos present in Johnson's Baby Powder and Shower to Shower?
A. Yes.
Q. And -- and what is that evidence?
A. Blount found asbestos in Johnson & Johnson's Baby Powder. Her report is in 1991. Her deposition specified that it wasn't just any talcum powder; it was Johnson & Johnson's.
Exhibits formerly known as 28, but now known as -- no. Are you kidding? It's 28 again -- showed tremolite, actinolite, and chrysotile -- chryso- -- in Shower to Shower.
Do you want me to go through every one of them, or just --
Q. Not every one, but --
A. Okay. But Johnson & Johnson sent -- some Johnson & Johnson samples had identifiable asbestos

fibers.
And the now labeled Exhibit 27 by Pier from -- deposition of Pier had Johnson & Johnson sample demonstrating chrysotile and tremolite.
Q. And is there also published literature that -- in addition to Dr. Blount that reports finding asbestos in cosmetic powders?
A. Yes. Those references are listed in the very first sentence of my section on asbestos in my report on page 18.
Q. And are you referring to --
A. Cralley.
Q. Is that -- would you spell that for the record?
A. C-r-a-l-l-e-y is the first author. 68.
Do you want me to pull all these studies and go through here for you?
Q. No.
Would it be fair to say that in addition to Dr. Longo's testing and the evidence that you've referenced in regard to the -- to the Hopkins chart and the Pier chart that there's evidence in the published literature regarding the presence of asbestos in talcum powder?

A. Yes.
MR. JAMES: Object to form.
Q. (BY MS. O'DELL) You were also asked earlier today about your review of the literature regarding the causal connection between exposure to asbestos and ovarian cancer.
Do you recall those questions?
A. I do recall those questions.
Q. Was your review of the asbestos and ovarian cancer literature comprehensive?
A. To the best of my ability.
Q. And you spoke earlier about the IARC monogram regarding asbestos and fibrous talc or a talcum asbestiform habit 100C -- you called that?
A. Yes.
Q. Do you --
MR. JAMES: Objection; form.
Sorry, Leigh.
MS. O'DELL: Excuse me.
Q. (BY MS. O'DELL) Did you review all of the monograph? Let me start there.
A. Yes.
Q. Did you review all of the articles that are referenced in IARC's comprehensive review of

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asbestos?
A. I read them.
Q. Did --
A. And other studies that have come out subsequent to IARC.
Q. Did you attempt to review all the relevant literature regarding asbestos and ovarian cancer?
A. I did.
Q. Is that literature included on the materials considered list that I think is Exhibit C of your expert report?
A. I believe all those references are in there.
Q. Has IARC concluded that fibrous talc or talc in an asbestiform habit is a known human carcinogen?
MR. JAMES: Object to form.
A. Yes.
Q. (BY MS. O'DELL) Now, I asked you just a moment ago about Exhibit C, the materials considered list, the -- the bigger list of literature that's --
A. This (indicating)?
Q. Yes -- included in your report.
And did you review the materials that

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are listed on Exhibit C?
A. I can't promise you that I've read every single word on every single study, but I have read the vast majority of them.
Q. Let me --
A. Greater than 90 percent.
Q. Okay. Let me switch gears for a moment. You were asked a series of questions today about the FDA's response to the civil service petition. That was one topic.
Do you recall that?
A. Yes.
Q. If you don't mind finding that and pulling it out. I think it's right here. It was Exhibit 8.
A. Yes.
Q. Do you recall that?
A. Yes.
Q. And if you will turn to page 5 of Exhibit 8. Just let me know --
A. This is the FEC letter.
Q. Yes.
A. Yes.
Q. And so if you'll look about a little more than halfway down the page, the paragraph beginning

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"While there exists."
Do you see that?
A. Yes, I do.
Q. And I think you and counsel for Johnson & Johnson discussed this a little earlier. It says, "The potential for particulates to migrate from the perineum and vagina through the peritoneal cavity is indisputable."
Did I read that correctly?
A. You did.
Q. Is that your opinion?
A. Absolutely.
Q. And counsel for Johnson & Johnson suggested that that statement in this letter that's written by the FDA did not apply to talc and talc migrating through the upper genital tract.
Do you recall that?
MR. JAMES: Object to form and object to the mischaracterization.
A. I recall that.
MS. O'DELL: It was not a mischaracterization.
Q. (BY MS. O'DELL) What does the next sentence say regarding the migration of perineal

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talc?
A. I was just getting ready to say it's the very next statement that they said: (Paraphrasing.) It is, therefore, plausible that perineal talc -- other -- any -- they say (other particulate) can reach the endometrial cavity, fallopian tubes, ovaries, and peritoneum and may elicit a foreign body reaction, inflammatory response, but in some exposed women may progress to epithelial cancers.
Q. And in terms of -- of -- of migration, let me also ask you -- just keep that in front of you, but I'm gonna pull out what's marked as Exhibit 19, the Langseth paper. If you see it, maybe you can help me.
A. Yeah. I told you they're all messed up.
Q. They -- they are.
A. Here it is.
Q. Okay. Great.
And the -- in reference to Exhibit 19, earlier, counsel for J&J suggested that the -- the IARC Working Group authored this paper.
Do you recall that?
A. I remember he -- this is from the Cancer Registry of Norway and Harvard and Montreal and

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Stockholm and Finland.
Q. So this is not an official publication of -- of IARC. Fair?
A. No, it is not.
Q. And if you'll -- but the authors in this study, if you'll . . .
A. Yeah. I see here where they mention the working group.
Q. Yes. And, in fact, the authors of the -- of the study, to be fair, are part of the working group. Is that . . .
A. Correct.
Q. And if you'll look at page 1 of Exhibit 19 and if you'll -- the left-hand column, the -- it's the next to the last paragraph toward the end of the page, does the authors of the Langseth conclude that talc particles can migrate to the vagina to the peritoneal cavity and ovaries?
A. They document asbestos fibers -- well, first they say: (Paraphrasing.) It's known that particles and fibres that enter the body can migrate to distant organs. Asbestos fibres that are found in the ovaries exposed to asbestos, analogously following perineal application, talc part- --

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particles can migrate from the vagina to the peritoneal cavity and ovaries. A majority of women experience retrograde menstruation. And this also -- this suggests a mechanism by which talc particles can travel through the female reproductive tract to the ovaries.
Q. Is this part of the evidence that you relied on in supporting your opinion that talc particles applied to the -- to the perineal area can migrate to the upper genital tract, including the ovaries?
A. Yes, and the research that these statements are based on.
Q. Yes. And what other evidence do you rely on to support your opinion that talc can migrate to the ovaries?
A. I have a section called "Migration" in -- in my report. While I'm finding it, I'll start with the multiple human studies, which I weight more heavily -- or influenced me more strongly than studies in rodents that have shown particulate matter passing from the perineum into the peritoneal cavity.
And -- and as I'm looking through all

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the studies, I will cite S-j-ö-r-s-e-n, et al., Egli and Newton, et al., Hunes, Zerm- -- a Greek study with the e-r.
Q. Why don't you spell it for us?
A. Why don't I look at my bibliography. It's gotta be the last one --
THE VIDEOGRAPHER: We need to change --
A. -- if they're in alphabetical order.
THE VIDEOGRAPHER: -- the disk, like now, so if we can go off the record.
MS. O'DELL: I'm sorry. I didn't hear you.
THE VIDEOGRAPHER: The disk, I need to change it out. It finished a little earlier, so let me swap it out.
MS. O'DELL: Can she finish her answer or . . .
THE VIDEOGRAPHER: No because I have to switch it out. Sorry.
(A recess was taken from 7:56 p m. to 8:00 p.m.)
THE VIDEOGRAPHER: This marks the beginning of disk 5. Back on the record. The time

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is 8:00 p m.
Q. (BY MS. O'DELL) Dr. Smith, before we had to change the videographic tape, I had asked you what evidence you rely on to support your opinion that talc migrates from the perineum to the ovaries, and you were walking us through that.
So why don't you just take a step back and --
A. Did you get the reading from Langseth on the tape?
Q. I think we got that. Assume we got that and then go from there.
A. Okay. So there are a number of papers that look at migration of particulates.
First, talc was identified deeply embedded in the ovaries, 1971 by Henderson.
Egli and Newton had flushed carbon particles from the vaginal vault and that came out in the peritoneal cavity. These patients generally who were coming to abdominal surgery in some period of time, same day, next day, up to four days in these studies.
And so this -- particulates would be placed in the vagina, not propelled, but placed in

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the vagina, and then the peritoneal cavity was entered, washed to see if those particulates are there. So Egli and Newton did carbon particles.

Sjösten did glove powder.

There are studies from K-u-n-z, looks at micronized albumin particles placed in the vagina that are transported.

There's a recent study by Zermanitokis [sic] -- you have the spelling -- that looks at tubal transport. And the great thing about that study is that you can pass particles and demonstrate them by ultrasonography and actually live-action watch them go through the tube and study tubal motal- -- motility as they go towards the dominant ovarian part -- particle.

All these particles, a wide range of studies from very small particles to larger particles, the majority of them were approximating sperm size, which is, in length, 5 microns.

So I looked at all these studies and conclude that migration is real. There's -- a female genital tract is the path to the peritoneal cavity.

Dr. Woodruff gave his presidential

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address in 1979 talking about ovarian cancer resulting from unknown agents transversing the vagina, cervix, endometrium, fallopian tube, into the peritoneal cavity, surrounding the uterus and inciting ovarian cancer.

I think we're seeing in in vitro studies in the lab, as we study inflammation in ovarian cancers, we are seeing -- able to generate these studies at a molecular level without hurting women, but seeing what the effect of exposure to talc is on normal epithelial cells, fallopian tubes . . .

Q. Before you get so far into that -- I'm gonna ask you about that in just a moment, but let me just ask one question before we leave migration. It is the ability of talc applied to the perineum to migrate through the -- the genital tract to the ovaries.

Is that a hypothesis?

MR. JAMES: Object to form.

A. I think it is something that happens. It is -- it has been -- while I have not seen a paper that demonstrates talc, per se, has been transported through the internal genitalia and to peritoneal

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cavity, particulates of similar size, larger and smaller, have been demonstrated to do that. These are not motile; they're not flagellated. A particle can go from outside to inside.

There's no reason why talc shouldn't do it, and certainly we've seen talc deeply embedded in the ovary suggesting that that's how it got there.

Q. (BY MS. O'DELL) In fact, the evidence is so strong the FDA has concluded it's indisputable.

MR. KLATT: Objection to form.

Q. (BY MS. O'DELL) Has the FDA concluded that it's indisputable that talc can migrate from the perineum to the upper genital tract?

MR. JAMES: Object to form. Mischaracterizes the letter.

MR. KLATT: Misstates the testimony.

A. I think indisputable is the word that -- that Dr. Musser, deputy director for scientific operations, Center for Food Safety and Applied Nutrition, used in his letter to Dr. Epstein.

"The potential for particulates to migrate from the peritoneum [sic] and vagina to the peritoneal cavity is indisputable." That's the word

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he used.

Q. (BY MS. O'DELL) Okay. Let me ask you to go back to the topic you were -- had moved on to. I just wanted to finish migration, and you were talking about inflammation.

A. Yes.

Q. What evidence is there that talcum powder causes inflammation?

A. Well, when you go into -- when you go into the laboratory, you don't have to use the broad brush of inflammation. You can look at specific biochemical production or responses of molecules involved in that inflammatory cascade.

So Kahn showed that nanopart -- nanotalc particles stabilized TNF-alpha, which is a tumor necrosis factor alpha in human macrophages, which is one of the steps in the inflammatory cascade.

In fact, he found that the smaller -- the smaller of the pol- -- particle, the more the production of unstabilization of TNF-alpha as opposed to larger pol- -- particles.

Saed has, through the 2000s, looked at ovarian cancer cell lines upregulation of

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anti-inflammatory and pro-inflammatory enzymes in products. And then -- and he's written -- has a new book chapter on it with Nicole Fletcher and all the people in his lab.

And then has recently had a paper accepted that looks at the response of controls, normal ovarian epithelium, fallopian tube epithelium, normal, and three different cell lines of ovarian epithelial cancer cells in response to three different levels of -- of talc.

And looked at the production of pro-inflammatory enzymes, decrease in anti-inflammatory enzymes, increase in cell proliferation, decrease in apoptosis, and induction of single-nucleotide polymorphisms that are associated with carcinogenesis.

Before we had one paper where a researcher named Buzard had taken a memorialized normal ovarian cell line, exposed it to 5 milligrams per -- micrograms, I'm sorry, per milliliter to -- of talc, talcum powder, and this is scientific grade talc, this was not Johnson's Baby Powder -- and induced malignancy, as measured by the criteria of lack of adherence in semi-solid auger, which is a

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standard of maligat -- malignancy and; yet, she didn't do anything with it. She didn't cytologically evaluate it. She didn't -- she just said, "I made it a malignant."

So we have an example of malignant transformation that is documented by a pretty reliable basis if you query -- I can't say that, but she really didn't go far with it.

Saed is starting to really break it down, and he had a really remarkable dose response in vitro to 5, 50, or 100-microgram per mil talc in his changes.

MR. KLATT: Object to the narrative answer.

Q. (BY MS. O'DELL) Has -- in addition to the Buzard paper you mentioned and Dr. Saed's work over the last decade, have there been others that looked at talc and -- in cell cult -- culture and found evidence that talc produced inflammation?

MR. KLATT: Objection; mischaracterization.

MR. JAMES: Join.

A. Oh, Shulka. I forgot that study. That's a big one. Shulka -- Shulka, S-h-u-l-k-a, looked

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at -- at exposed normal mesothelial cells and then normal ovarian epithelial ovarian cells to both asbestos and nonfibrous talc and found induction of pro-inflammatory genes have -- with exposure to these 2 carcinogens.

Here's another Saed.

I think that covers it pretty much.

Q. (BY MS. O'DELL) You asked earlier today about I think the question was -- well, let me just ask it this way: Is there a regulatory body that shares your view that talcum powder can cause ovarian cancer?

MR. JAMES: Object to form.

A. The Canadian EPA, CEPA, came out with Health Canada, which is publishing under -- is in it's discussion period where they cite the literature and base -- and their conclusion is that talcum powders -- I can paraphrase it.

Do you have a copy that I can read?

But they say that talcum powder is a significant public health risk to women from perineal exposure, but I -- off the top of my head, I can't remember their conclusion to read to you.

Q. (BY MS. O'DELL) You also asked some

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questions today about the -- about ACOG.

Do you remember those questions about ACOG and the societies --

A. Um-hum.

Q. -- of which you're a member?

A. Um-hum.

Q. What's referred to as "The Green Journal," I believe?

A. It's obstetrics and gynecology. It's the journal of ACOG.

Q. And has -- recently have papers been published regarding ovarian cancer and its -- excuse me, and talcum powder causing -- well, let me strike that and start over.

Have recently, in The Green Journal, there have been a publication dealing with talcum powder products causing a significant increase in ovarian cancer?

A. I think what --

MR. JAMES: Object to form.

A. I think what you're referring to is, you know, the end of every year they -- they review a lot of topics and it's, you know, top five articles in preeclampsia and top five articles in

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endometriosis and there's Jason Wright wrote the top five articles in ovarian cancer.
And I think -- I don't remember whether they were ranked, but I know Number 4 on the list was the Penninkilampi study, but that's -- I don't know who decides that. I don't remember reading how that was decided, but I know Jason Wright wrote it.
Q. (BY MS. O'DELL) And is that something that suggests that the -- the causal connection between the use of genital talc and ovarian cancer is becoming more well-known in the medical community?
MR. JAMES: Objection to form.
MR. KLATT: Objection; leading. Speculation.
A. I think both Canada Health and the flurry of two publications in '18. There are other studies that are ongoing and in various stage of analysis, preparation, proof, shows that we're getting a lot more interest in talc and its relationship to ovarian cancer. And there is increasing concern in the -- all over the world, but the studies I know of are largely in the United States and Canada.

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Q. (BY MS. O'DELL) Let me change topics just for a minute.
You were asked questions throughout the day, different points about the fragrance chemicals that comprise the fragrance for -- fragrances for Baby Powder and Shower to Shower.
Do you recall that?
A. I do recall that.
Q. Do you -- did you -- excuse me.
Do you defer to Dr. Crowley on his examination of the specific characteristics of those fragrance chemicals?
A. I was getting ready to say I defer -- before you could finish your sentence. I defer to Dr. Crowley on everything about fragrances.
Q. And do you -- I mean, your -- do you rely on his opinions regarding the inflammatory, toxic, and potential carcinogenic effect of the chemicals in the fragrances for Baby Powder and Shower to Shower?
A. Yes. I don't know anything about those substances.
Q. You were also asked questions about the heavy metals that had been demonstrated to be

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present in talcum powder in certain periods.
MR. JAMES: Object to form.
Q. (BY MS. O'DELL) Do you rely on IARC's comprehensive review of the literature regarding the carcinogenicity of chromium?
A. Yes.
Q. Did you review IARC's analysis of --
A. Yes. I read that. That is the way I made my assessment of whether or not they are toxic.
Q. And did you -- in the same way, did you review IARC's Monograph in relation to nickel?
A. Yes.
Q. And do you rely on IARC's comprehensive review of both the epidemiological literature, the animal studies, and other evidence regarding the carcinogenicity of nickel?
A. Yes.
Q. And --
A. I didn't individually pull every one of their papers. I just read IARC.
Q. And you relied on IARC's review of those materials?
A. Yes. I have trusted them. If they say nickel is a carcinogen at specific levels, then I

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have no intention of pulling all those papers and studying them myself.
Q. And would the same be true of Cobalt?
A. Yes.
Q. I want to show you what I'm going to mark as Exhibit 30, and this is a copy of the Berge paper. It's the most up-to-date copy.
(Deposition Exhibit 30 marked for identification.)
Q. (BY MS. O'DELL) So I've handed you Exhibit 30. It's a copy --
A. Um-hum.
Q. It's the most up-to-date copy of the Berge paper. We had discussions today at different times. I think that we had different Berge publications, and so I want to mark the one that has been published most recently.
A. Okay. This is -- we have previously marked the e-Pub. This is the print.
Q. All right. And if you'll -- I have just one question.
You were asked today or the suggestion was made to you today that in Berge the study did not demonstrate a dose response.

Do you recall those questions?
A. Yes.
Q. And if you'll take a look at the next to last sentence of the abstract --
A. Yes.
Q. -- of Berge.
Do you see that?
A. Yes.
Q. And, in fact, did Berge demonstrate a -- a dose response?
A. He says it's a -- which appears to be limited, that -- okay.
"Statistically significant association between general use of talc in ovarian cancer, which appears to be limited to serous carcinoma was suggestion of dose-response."
Q. The . . .
A. And he has a table of the duration frequency.
Q. And is that table supportive of the fact that the studies show the -- a dose response or at least the trending of a dose response?
A. Their -- the --
MR. KLATT: Objection.

MR. JAMES: Object to form.
A. His results -- his relative risks are 1.16 for a duration. 1.05 for frequency. They are statistically significant with 1.07 to 1.26 for a duration. 1.04 to 1.07 confidence intervals. But his number of risk estimates are small, 12 and 7.
Q. Okay. You . . .
MR. JAMES: Leigh, if you're done with Exhibit 30, may I have a look at it, please.
MS. O'DELL: Sure.
A. I think -- from what I've seen, it looks pretty much the same.
MR. JAMES: Thank you.
Q. (BY MS. O'DELL) Let me ask you to --
A. Except that chart is -- oh, yeah. It's in the other one. Down here. I think they're the same thing.
Go ahead.
Q. Doctor, you were asked a series of questions about individual patients and whether talcum powder can cause ovarian cancer in an individual patient.
Do you remember those questions?
A. Generally.

Q. Yeah. Have you been asked to look at any individual patients in order to render what's ter- -- referred to as a case specific opinion?
A. No.
Q. And is it -- would you be willing to do that if asked?
A. No. I haven't thought about it.
Q. Okay.
A. I'd like to think about it before I accept any more responsibility.
Q. Yeah.
Does that in any way --
A. At this hour -- at this hour of the deposition.
Q. Does that in any way undermine or change your opinion that talcum powder products, Baby Powder and Shower to Shower cause ovarian cancer?
A. No.
MR. KLATT: Objection; leading.
A. It doesn't change my mind.
Q. (BY MS. O'DELL) And is that opinion based on your review of the totality of the literature as you've described in your report and in the materials that are cited not only within the report but also

Exhibit C?
MR. JAMES: Object to form.
A. Yes. I -- I find the epidemiologic data and the consistency is so significant, and then the biochemical stuff, the skin would be coming out like gangbusters. Speaks to plausibility, experimentation, mechanism, and that's just very compelling.
Q. (BY MS. O'DELL) And in terms of the opinions that you've expressed in your report, are those opinions based on the published literature and other data that you have referenced and relied on in your report?
A. Yes.
Q. Okay.
A. All of that has been published and peer-reviewed.
Q. Right.
So the degree that there's new data coming out, you're not relying on sort of the hope of new data in the future to reach your opinions?
A. No, I think I'm willing to commit and make my opinion. I -- I feel very excited that we have -- we will have opportunities as we understand

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this process, the therapeutic interventions at some time.
Q. You were asked questions earlier today about what you had done prior to litigation and what you've done post litigation in terms of informing your opinions in this case.
Did you know that talc and asbestos are inflammatory prior to becoming involved in the litigation?
A. Yes.
MR. JAMES: Object to form.
Q. (BY MS. O'DELL) Prior to the litigation, did you know, based on your understanding of the medical and scientific literature, that inflammation creates a pro-carcinogenesis -- excuse me, carcinogenic environment?
MR. JAMES: Object to form.
A. Yes.
Q. (BY MS. O'DELL) Prior to the litigation, did you know, based on your review of the scientific and medical literature, that inflammation was a mechanism for epithelial ovarian cancer development and progression?
MR. JAMES: Object to form.

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A. Certainly the recent data is more compelling, that has been postulated, and various little snippets of data like some of Saed's stuff and enzyme induction, stuff like that, has been leading there. It's been growing.
Q. (BY MS. O'DELL) But you were aware of that --
A. Yeah, prior to --
Q. -- in -- excuse me. You were aware of --
A. -- prior to January of 2017.
Q. Okay.
MR. JAMES: Object to the form.
Q. (BY MS. O'DELL) Prior to litigation, did you know that particles such as talc and asbestos could migrate or be transported to the fallopian tube and ovary from the perineum?
MR. JAMES: Object to the form.
A. Oh, yes.
Q. (BY MS. O'DELL) Prior to the litigation, were you aware of scientific data and medical literature demonstrating that talc as well as asbestos could be exposed to the body through inhalation?
A. Oh, yes.

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Q. Are your opinions in this case outlined in your deposition today as well as the report that you've provided in this case?
A. Yes.
Q. And every time today when you have referred to talcum powder products, have you been referring to Johnson's Baby Powder and Shower to Shower?
MR. JAMES: Object to form.
A. Except when specified otherwise.
Q. (BY MS. O'DELL) Okay. And then last question. You were asked a series of -- or maybe the last question.
You were asked a --
A. I got so excited.
Q. We've got a series of questions about what you tell your patients, and you --
A. Um-hum.
Q. -- testified that you do not tell your patients presently about the increased risk of ovarian cancer with perineal talc use.
Do you recall that?
A. I do.
Q. Do you treat patients with ovarian cancer

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at this time?
A. At the end of their life.
Q. Why do you not tell them about talc as a -- as a cause of ovarian cancer?
A. It's too late.
Q. Why?
A. They're dying.
Q. And --
A. There's nothing -- they failed all therapy. If there was adequate therapy --
Q. And it would be --
A. -- to reverse it, then they wouldn't be my patient.
Q. And it would be insensitive and wrong to counsel a patient at that junction in their life --
A. Um-hum.
Q. -- about a risk factor that they will have no effect on their --
A. They can't do anything about it. I don't want to induce guilt. The horse is out of the barn.
They need pain control.
They need nausea control.
They need love, support. They need their family, you know, their priest or spiritual

leader. They need a lot of care, but they don't need to be told "This happened because you used powder" or, "Boy, if you hadn't" -- I don't know. That'd be just dumb.

MS. O'DELL: I don't have any further questions, Dr. Smith. Thank you.

I'm sure these -- one of these gentlemen will have some questions.

MR. JAMES: We will.

Are we taking five, Mike?

MR. KLATT: Five minutes.

MR. JAMES: Okay.

MR. KLATT: We'll just need a time from the videographer.

MR. JAMES: Okay.

THE VIDEOGRAPHER: So let's -- are we going off?

MR. KLATT: We don't need to go off. Just what's the time?

THE VIDEOGRAPHER: 32 plus 16 prior, so it should be 48.

MS. O'DELL: So I'm not sure what the -- I'm not sure what the calculation's being made.

MR. SILVER: Let's go off the record so we can figure out the calculation because I think it's different that he . . .

THE VIDEOGRAPHER: Going off the record. The time is 8:32 p m.

(A recess was taken from 8:32 p m. to 8:43 p m.)

THE VIDEOGRAPHER: Back on the record. The time is 8:43 p m.

FURTHER EXAMINATION

BY MR. JAMES:

Q. Dr. Smith, good evening.

A. Hi.

Q. I have a few more questions for you. Okay?

A. Okey-doke.

Q. Are you aware of any studies or literature showing that the presence of heavy metals in cosmetic talc powders increases the risk of ovarian cancer?

MS. O'DELL: Object to the form.

A. I know that IARC calls those Class 1 -- two of them Class 1 carcinogens. I don't know how much they influence the carcinogenicity of talcum

powder.

Q. (BY MR. JAMES) Are you aware of any scientific literature or studies that address whether the chemicals and the fragrances of talc powder cause ovarian cancer?

A. I do not. I defer to Dr. Crowley.

Q. Did you consider the body of literature, looking at whether talc is associated with other types of gynecological cancers?

A. I did not --

MS. O'DELL: Object to the form.

A. I did not even search endometrial cancer, cervical cancer, vulvar cancer.

Q. (BY MR. JAMES) Do you believe that body of literature would be relevant to the opinions you're offering today?

A. It would be confirmatory, were it to exist.

Q. Confirm --

A. I don't know if it exists.

Q. Sorry.

Confirmatory to the extent that it revealed an association, correct?

MS. O'DELL: Object to the form.

A. To the extent that it revealed an association if such literature exists.

Q. (BY MR. JAMES) If the literature, looking at the association between talc and other gynecological cancers, did not support an association, would that impact the opinions you're offering today?

MS. O'DELL: Object to the form.

A. Probably not.

Q. (BY MR. JAMES) Why is that?

A. Because -- because of the lethality of ovarian cancer, we do much better curing endometrial and cervix cancer. Ovarian cancer is a real killer. Not that I want anybody to get cancer.

Q. And I'm not sure that I understood your answer.

A. Okay.

Q. So -- and it may -- and it's probably on my part.

But you said because of the?

A. Lethality. Lethal.

Q. Lethality? Lethality. Okay.

A. Yeah, of ovarian cancer. It is unusual to -- it's unusual to find ovarian cancer at an

early stage. It is unusual to cure ovarian cancer. We have a pretty darn good -- well, it could be better. We don't cure everybody. But we have a pretty good track record with curing endometrial and cervical cancer. Not that I want anybody to get cancer, but we need to do everything to decrease the incidence of ovarian cancer.

Q. If your opinion is that talc causes ovarian cancer, would you believe that talc would also cause cervical cancer?

A. I don't know that information.

MS. O'DELL: Objection; form.

A. Cervical cancer -- cervical cancer, in all, except extremely rare incidents such as DES exposure, which thank God we've gotten rid of, is -- a component of cervical cancer is human papilloma virus, which is a necessary but insufficient carcinogen. That is, this is your cumulative -- one of your cumulative examples where you've got to have the one of HPV, but then you need another punch. You need another factor. You can't just have HPV to cause cervical cancer.

I -- I can't think of any research that -- in influence of talc usage in cervical

cancer. I don't think I've ever seen that paper.

Q. (BY MR. JAMES) Would you expect talc to be associated with uterine cancer?

A. I've never seen that paper either. Taking us back to Mr. -- is it Klatt? Menstruation association -- I'm just -- I'm thinking, and I shouldn't be thinking. I should -- I've never seen that paper.

Q. Or body of papers, if such a body exists, correct?

A. Or if such a body --

MS. O'DELL: Object to the form.

A. -- exists.

Q. (BY MR. JAMES) You would agree that if talc migrates to the genital tract, that talc would be exposed to tissues and organs along the way, correct?

A. Yes.

Q. Okay. You discussed with your counsel Exhibit Number 30, which is the most recent version of the Berge paper, correct?

A. Yes. I have the -- I have the 24, but I think this is good enough.

Q. And I'm gonna hand you back Exhibit 30.

A. Okay. I haven't found any differences between the two, except the page numbers.

Q. And Dr. Smith, if you could just look at that abstract for me on the first page, please.

A. Yes.

Q. And you see at the bottom of the abstract that -- the sentence that I asked you about earlier, and discussed with you at some length, about the heterogeneity issue.

Do you see that?

A. Yes.

Q. Okay. And you see there that the authors of the Berge paper still conclude on Exhibit Number 30 that a causal interpretation is not warranted, correct?

MS. O'DELL: Objection; form.

A. It says, "The heterogeneity" -- they didn't say it's not causal. They say the heterogeneity results detract from a causal interpretation, so that lowers the chance that they're willing to make in a causal association. It doesn't strike it out entirely.

Q. (BY MR. JAMES) And that language is consistent with the language that we discussed

earlier today, correct?

A. It is.

MS. O'DELL: Objection; form.

Q. (BY MR. JAMES) During counsel's questions, you made references to literature or studies that I think you characterized as "would be coming out."

Is that terminology that I heard correctly?

A. Yes.

Q. Okay. Are you aware of studies on the talc ovarian cancer hypothesis that are works in progress?

A. Yes.

Q. Okay. What are those studies?

A. Well, there's another epidemiologic study cited in Health Canada by Traher -- Taher, T-a-h-e-r, Mohamed Taher, and a whole bunch of other people. That is another epidemiologic meta-analysis.

Q. Are there any other studies that you're aware of that pertain to the issues in this litigation that are works in progress?

A. I think people all over are still actively

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looking at inflammation in all cancers at various molecular levels. Gosh. Their group's called the Cancer Genome Analysis, that's working on -- continues to work on ovarian cancer. Sambucetti looks on ovarian cancer with BRCA mutations. Looking -- there are new papers coming out all the time on other risk factors.
Q. And if I may ask a very precise question in hopes of moving us along.
A. Okay. Sorry.
Q. That's fine.
A. No worries.
Q. Are you aware of any other papers that are works in progress that specifically look at the issue of talc and ovarian cancer?
A. I have not read --
MS. O'DELL: Besides the one she mentioned?
A. Besides the one I mentioned, I have not read any other data or prepublication drafts.
MR. JAMES: Okay. That's all the questions I have for now.
MR. KLATT: Oh.
THE WITNESS: What are we on? 10s?

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14, 13. It may be down here. 11, 10.
MR. KLATT: Do you -- I don't -- I'm looking for the IR Asbestos Monograph.
THE WITNESS: This is not it?
MR. KLATT: No, I don't believe so.
THE WITNESS: I mean, it's like --
MS. O'DELL: I don't believe we entered that yet.
THE WITNESS: It's got -- this is from the IR Monograph, but it is not the --
MR. KLATT: Do you have the entire monograph --
THE WITNESS: Yes, we do.
MR. KLATT: -- in one of those books?
THE WITNESS: Yes, we do.
MR. KLATT: Can you pull it?
THE WITNESS: Second IA.
MS. O'DELL: Which monograph?
THE WITNESS: The --
MR. KLATT: The 2012 Asbestos Monograph.
THE WITNESS: MC. It's the second one. It's not that one. It's the second IA. Yep, that's it.

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MR. KLATT: Let me do this.
Let's just mark this, the full Asbestos Monograph --
THE WITNESS: Okay.
MR. KLATT: -- Doctor, instead of some pages. Let's mark it as the next exhibit.
THE COURT REPORTER: It should be 31.
(Deposition Exhibit 31 marked for identification.)
FURTHER EXAMINATION
BY MR. KLATT:
Q. Doctor, I'm handing you, and just verify it's what you're looking at. But this -- I'm representing to you this is a copy of the 2012 IARC Asbestos Monograph that's referred to your report and also --
A. Exactly.
Q. -- referred to in your testimony multiple times today, correct?
A. Correct.
Q. And if you would, turn to page 256, please.
A. (Complied.) Getting close.
Q. Are you at page 256?

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A. I am.
Q. Of the IARC 2012 Asbestos Monograph?
A. I am.
Q. I'm looking in the right-hand column, and I think you looked at this language earlier today.
The right-hand column, the middle paragraph says, "The IARC Working Group noted that a causal association between exposure to asbestos and cancer of the ovary was clearly established based on five strongly positive cohort mortality studies of women with heavy occupational exposure to asbestos," correct?
A. Correct.
Q. And then it cites five studies that you've reviewed, correct?
A. Right.
Q. None of those studies involve the type of asbestos that's alleged to be in Johnson & Johnson's body powder products, correct?
MS. O'DELL: Object to the form.
A. I'd have to look at them back to look at the types. I -- I'm sorry. I don't remember the details in these studies --
Q. (BY MR. KLATT) If, in fact --

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A. -- at the time.
Q. -- those five studies involve a type of asbestos that hasn't been alleged to be in Johnson & Johnson's Baby Powder, then you wouldn't be reliant on those, correct?
MS. O'DELL: Object to the form. Misstates the record.
A. These studies are not about Johnson's Baby Powder.
Q. (BY MR. KLATT) Exactly.
A. These studies are about asbestos.
Q. Right. And they're not even done in the U.S., are they?
A. Some of them for sure were in the UK. I can look them all up if you want.
Q. And they were studies of women who had heavy occupational exposure to asbestos, correct?
That's what the IARC Monograph says?
A. I can -- I can look at that in more detail if I find Reid or --
Q. No, I'm just asking you what the IARC Monograph says.
MS. O'DELL: You're welcome to refer to Reid if you'd like.

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A. I'd like to refer to Reid if I can find it, because it's up here as evidence. Early, early --
Q. (BY MR. KLATT) But I'm not asking you about Reid. I'm asking you about the IARC Monograph.
A. The Reid includes those studies in a meta-analysis and has details on those studies that will allow me to refresh my memory --
Q. All right. I'll withdraw --
A. -- about them.
Q. -- the question.
I want to focus on what IARC's saying because you said earlier today you relied on IARC.
IARC says in Exhibit 31, Doctor -- IARC says in Exhibit 31 that the link to ovarian cancer and asbestos is based on the studies with women with heavy occupational exposure, correct? That's --
A. Predominance, it says that. And the predominoc- -- the predominant exposure in these studies, to my memory, was occupational. But I believe some -- some studies were spouses and -- of people who were nonoccupationally exposed, and I

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can't remember which studies are that.
Q. I'm talking about the studies IARC is relying on for its conclusion that ovarian cancer --
A. I'd like to --
Q. -- is related to --
THE WITNESS: Get me Reid, will you? What is that saying on there?
Q. (BY MR. KLATT) The studies are cited right there, Doctor.
A. I know. I just --
MS. O'DELL: She's just reading.
A. -- was verifying the information before I give this to you.
(Examined exhibit.) Okay. My -- the next sentence takes us where we want to go.
(Paraphrasing.) The conclusion received these initial support from studies showing women and girls with environmental but not occupational exposure. I will give you that now.
Q. Okay. But it says the link is clearly established based on the heavy occupational exposure, correct?
MS. O'DELL: Objection to the form.
A. That was their initial establishment of

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the link.
Q. (BY MR. KLATT) Now, that very same IARC Monograph, turn over to page 280, if you would. It says there in the right-hand column about three paragraphs down -- do you see where I'm reading?
A. Yeah.
Q. This very same IARC Working Group that looked at asbestos says, "The association between exposure to talc, potential retrograde translocation to the ovarian epithelium, and the development of ovarian cancer is controversial," correct?
MS. O'DELL: Objection.
A. That was their assessment based on IARC 2010, which --
Q. (BY MR. KLATT) And this --
MS. O'DELL: Excuse me.
Q. (BY MR. KLATT) I'm sorry. Go ahead.
A. -- and this volume.
MS. O'DELL: She was not finished.
Q. (BY MR. KLATT) And this volume is --
MS. O'DELL: Excuse me.
A. And this volume.
MS. O'DELL: Let her finish, please, sir.

Q. (BY MR. KLATT) Are you finished?
A. I am now.
MS. O'DELL: She was not finished, and it's not gonna be clear on the record.
Dr. Smith, if you need to finish your answer, please go ahead and do that.
Q. (BY MR. KLATT) I apologize. I thought you were finished, and so I didn't mean to interrupt you.
So IARC, on the one hand --
THE WITNESS: I said it.
Q. (BY MR. KLATT) -- is saying --
THE WITNESS: She's got it down.
MS. O'DELL: Okay.
Q. (BY MR. KLATT) I'm sorry?
A. The transcriptionist has what I said. This -- 20 -- 93 and 100C, 2010 and 2012.
Q. Are what IARC cites for stating that the association between exposure to talc, potential retrograde translocation to the ovarian epithelium, and the development of ovarian cancer is controversial, correct?
MS. O'DELL: Object to the form.
A. That's what they say in probably 2011.

Q. (BY MR. KLATT) So on the one hand, they're saying in this monograph that the link to ovarian cancer they ascertain is based on every occupational exposure, but when they describe the association with talc, retrograde translocation to the ovaries and ovarian cancer, they don't say it's clearly established at all. They say it's controversial, correct?
MS. O'DELL: Object to the form.
A. I know what they say. I can read their words. I would, again, disagree that retrograde translocation of particulates to the ovarian epithelium is not controversial based on the data that I've been talking about for about half the day.
Q. (BY MR. KLATT) Which IARC also summarizes in its 2010 talc monograph and in this monograph?
A. In 2010 --
MS. O'DELL: Objection -- excuse me. Excuse me.
Objection. That is -- misstates her prior testimony, and you know that.
So to the degree you understand the -- the question, Dr. Smith, please go ahead.
A. I know what they say. I know what I have

facts to substantiate. They are not the same thing, so I disagree with their assessment that retrograde translocation to the ovarian epithelium is at all controversial for any particulate.
I have talked about the both epidemiologic and biochemical by different investigators of exposure to talc in vitro and a strong epidemiologic history relating talc and ovarian cancer.
So based on what I've been talking about for the past 12 hours, I disagree with this.
Q. (BY MR. KLATT) Okay. Well, that's what I wanted to establish.
On the one hand, when IARC in the asbestos monograph in 2012 is talking about exposure to talc, translocation to the ovaries, and the development of ovarian cancer, they don't say it's clearly established at all.
They -- they, IARC, says it's controversial, correct?
MS. O'DELL: Objection; asked and answered.
A. They're flat wrong.
Q. (BY MR. KLATT) I'm asking what IARC says.

A. I -- okay. We have read this sentence 14 times.
Q. Do you agree with it?
A. I do not agree with the statement. I agree those words are printed on the paper.
Q. Do you agree that's IARC's position?
A. IARC printed those things --
MS. O'DELL: Objection; asked and answered.
A. -- and said that.
Q. (BY MR. KLATT) Okay. Thank you.
And they cite their own talc monograph in 2010, and they cite their asbestos monograph --
A. Asked and answered.
Q. -- and they ask -- you're not the lawyer here.
A. I know it, but I'm getting it.
Q. IARC, for the statement that the exposure to talc translocation to the ovaries and development of ovarian cancer is controversial, what IARC cites -- listen to me, Doctor -- what IARC cites --
A. I'm listening. I have my eyes closed, but I'm listening.
Q. -- is their own 2010 talc monograph and

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this very 2012 asbestos monograph, correct?
MS. O'DELL: Excuse me. Asked and answered 10 times.
Q. (BY MR. KLATT) Is that correct?
MS. O'DELL: Excuse me. Asked and answered.
A. The words are printed on the paper. That is what they wrote.
Q. (BY MR. KLATT) So my statement's correct?
MS. O'DELL: Objection.
A. They wrote that, yes.
Q. (BY MR. KLATT) Not that hard.
I think we established earlier that there's not a single study showing talc applied to the external genital area has been shown to migrate into the ovaries?
A. I know of no talc translocation migration studies.
Q. And the Egli study and the Sjösten study and the Zervomanoklakis study --
(Speaking simultaneously.)
A. I'm not (unintelligible).
Q. -- that you cited, none of those involve talc?

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A. None of --
MS. O'DELL: Object to the form.
A. -- them did.
Q. (BY MR. KLATT) And they all involve those particles being injected into the reproductive tract?
MS. O'DELL: Object to the form.
A. Absolutely not.
Q. (BY MR. KLATT) They say poster- --
A. Sjösten did not inject anything. He had corn starch on gloves.
Q. And was that applied externally or was the corn starch --
A. It's a pelvic examination.
Q. Let me finish.
And a pelvic examination involves introduction of corn starch on surgical gloves into the reproductive tract. It's not specific --
A. I don't think you'll get any --
MS. O'DELL: Excuse me. Excuse me.
Q. (BY MR. KLATT) It's not external application, correct?
MS. O'DELL: Object to the form.
A. You said "injected."

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Q. (BY MR. KLATT) Okay. Well, let's talk -- Egli and Zervomanoklaskis involved injections of particles into something called the vaginal posterior fornix, correct?
A. Um-hum.
Q. I'm sorry?
A. Yes.
Q. And that's not the external genital area, is it?
A. Hum. That is part of the lower genital tract.
Q. The posterior vaginal fornix is the area of the vagina right next to the cervix, correct?
A. Uh-huh.
Q. So the very top of the vagina, correct?
A. It's sort of at the very back.
Q. And so it's not at the external genital area, correct?
A. I didn't say it was external. I said it was part of the lower genital tract.
Q. It's about halfway to the ovaries, correct?
MS. O'DELL: Objection to form.
A. Yes.

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Q. (BY MR. KLATT) And those animals in those studies --
A. They're humans.
Q. Well, no. You said -- Egli, I thought you said was in animals.
MS. O'DELL: Object to form.
A. No, Egli's in humans.
Q. (BY MR. KLATT) Well --
A. Egli's --
Q. -- the humans were --
A. -- in humans.
Q. The hum- --
A. Zervomanoklaskis is in humans. Sjösten is in humans. Hunts is in humans.
Q. And these humans, then, were given Pitocin to stimulate uterine contractions, weren't they?
A. Some of them in some of the studies.
Q. Well, that doesn't have anything to do with women applying talc externally, does it?
MS. O'DELL: Object to the form.
A. No, but it is part of the transport mech- -- the contractions of the uterus and the fallopian tube are part of the mechanisms of transport.

Q. (BY MR. KLATT) And, in fact, in Egli, the -- the study subjects were tilted head down at a 15-degree angle, correct?
MS. O'DELL: Objection to form.
A. Yes.
Q. (BY MR. KLATT) And in Sjösten, it was corn starch, not talc, correct?
A. Yes.
Q. And you said these were a part of gynecologic examinations in which the physician was introducing the corn starch into the reproductive tract, correct?
MS. O'DELL: Objection to form.
A. On his or her gloves. Not injecting it.
Q. (BY MR. KLATT) Health Canada that you've referred to, they just announced a preliminary evaluation and opened it up to public comment, right?
A. They are in the 90-day discussion window.
Q. And -- well, the discussion window means the public comments can be submitted for the next 90 days, correct?
A. Correct.
Q. And then they have up to two years to make

a decision whether they're gonna do anything at all or nothing, correct?
MS. O'DELL: Object to the form.
A. Correct.
Q. (BY MR. KLATT) So they haven't made any final conclusions at all, have they?
A. They've drawn their conclusions. They will entertain comments. I think their conclusions are compelling.
Q. Well, at the end of nine -- at the end of two years, they may decide to do nothing at all based on the evidence they receive, correct?
A. It might, but may still be here.
Q. The Shukla study that you talked about --
A. Yes.
Q. -- that didn't look at any sort of genetic mutations, did it?
A. It looked at gene activation.
THE WITNESS: Can you get the Shukla?
Q. (BY MR. KLATT) Gene expression, correct?
A. Gene expression.
THE WITNESS: Sorry. Thank you.
Q. (BY MR. KLATT) Gene expression is a part of daily living, isn't it?

MS. O'DELL: Object to the form.
A. Gene expression is part of everything.
Q. (BY MR. KLATT) Exactly. It's how we live.
If we didn't have gene expression, we'd die, right?
A. Right.
Q. So the mere fact that they measured gene expression doesn't say anything about causing cancer, does it?
A. It's what genes --
MS. O'DELL: Object to the form.
A. -- they looked at.
Q. (BY MR. KLATT) And Shukla didn't conclude that their findings showed that talc causes ovarian --
MS. O'DELL: Give her a moment to --
Q. (BY MR. KLATT) -- cancer --
MS. O'DELL: -- and just --
Q. (BY MR. KLATT) -- correct?
MS. O'DELL: You may look at the study before you answer the question.
Q. (BY MR. KLATT) Well, you testified to Shukla study in response to Ms. O'Dell's question

without looking at it.
MS. O'DELL: Let me rephrase my objection.
If you need to look at a study, you may. If you don't, please feel free to answer Mr. Klatt's questions.
Q. (BY MR. KLATT) Doctor, when you were answering Ms. O'Dell's questions about Shukla, you didn't need to look at the study, did you?
MS. O'DELL: Objection.
A. I want to know -- I want to see the descriptions of --
Q. (BY MR. KLATT) Did they conclude their results of their study showed that talc caused ovarian cancer?
A. (Examined exhibit.) So they looked at -- this is the mesothelioma, so we're not -- they looked at subalteration, cell activation, cell motility, immune response, protein metabolic processes, signal transection, changes in extracellular matrix.
All of these are pathways looking at MRA levels that are activated in the carcinogenic process in . . .

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Q. Doctor, my question is: Shukla nowhere concludes that the results of their experiments showed that talc or even asbestos caused ovarian cancer, correct?
A. No, they did not cause ovarian cancer, yes.
They upregulated enzymes active in some part of the carcinogenic process. They didn't induce any demonstrated genetic abnormalities.
Q. Correct.
And if you would turn your attention to page 2000 -- I'm sorry. Page -- do you have a page 121?
A. No -- oh, wait. I have a -- this is crazy. I have a 199 and then it goes to 2009 -- oh, wait. That may be the year.
Q. I think that's the year.
A. Yeah, I think that's the year.
Ah. I have a 121, yes.
Q. Okay. Do you see a paragraph in the Shukla study on page 121 beginning with, "Several other genes"?
A. Yes.
Q. "Several other genes uprate -- upregulated

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by talc at 8 hours are affected by asbestos at both 8 and 24 hours may be important in repair from mineral-induced responses," correct?
A. Correct.
MS. O'DELL: Object to the form.
Q. (BY MR. KLATT) For example, SOD2 is an antioxidant protein, correct?
A. Correct.
Q. Antioxidant has anticancer properties, right?
MS. O'DELL: Object to the form.
A. In general.
Q. (BY MR. KLATT) And you see that the next thing they talk about, PTGS2?
A. Yes.
Q. It's a key enzyme in pros- -- prostanoid bio- -- biosynthesis associated with modulation of mitogenesis and inflammation, correct?
MS. O'DELL: Object to the form.
A. Correct.
Q. (BY MR. KLATT) That's an anticancer property?
A. Not necessarily.
Q. Well --

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A. You can modulate up and you can modulate down.
Q. And what they found is that it modulated down, correct?
MS. O'DELL: Object to the form.
A. I don't see the figure.
Q. (BY MR. KLATT) Do you see the next thing they talk about? Upregulation of angiopoietin-4.
A. Um-hum.
Q. Do you see that?
A. Uh-huh.
Q. Is thought to play a key role -- or excuse me, play a role in inhibition of tumor cell motility and metastasis.
So if you're inhibiting tumor cell motility and metastasis, that's an anticancer property, correct?
MS. O'DELL: Objection to the form.
A. Yes.
Q. (BY MR. KLATT) And then KLF4, Kruppel-like factor 4, is a negative regulator of cell proliferation, correct?
A. And can be a positive or negative modulator of DNA transcription.

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Q. Well, cancer is uncontrolled cell proliferation, correct?
A. You can't -- it can go either way.
Q. Well, it says --
MS. O'DELL: Excuse me. She's finished?
Q. (BY MR. KLATT) -- it's a negative regulator of cell proliferation.
Does it say that?
A. Which is different from transcription. It says "positive or negative transcription."
Q. But if you're a negative regulator of cell proliferation, that's an anticancer property, correct?
MS. O'DELL: Objection to form.
A. I think --
MS. O'DELL: She's answered the question.
A. -- that's oversimplified.
Q. (BY MR. KLATT) What a negative regulator of cell proliferation means it down-regulates self-proliferation, correct?
A. Yes.
Q. That's anticancer property?

A. I think when you make that big jump, there are a whole lot of little steps in there to get to that.
I can't make that conclusion, and I don't think you can either.
Q. I'm just reading what they're saying there.
MS. O'DELL: Object to the form.
A. No, you're interpreting what they're saying because they didn't say it's an anticancer drug.
Q. (BY MR. KLATT) They say it's a negative regulator of cell proliferation, correct?
A. And nowhere in this sentence does it say it's anticancer.
Q. Well, do you want something that increases cell proliferation or decreases cell proliferation?
A. Certainly in repair --
MS. O'DELL: Objection to form.
A. -- process. If it's normal epithelium, I want -- you don't know enough about this and neither do I.
Can we just keep going?
Q. (BY MR. KLATT) Sure. That's fine.

You're not aware of any evidence that genital talc use increases vulvar cancer in women --
A. No.
Q. -- who use it, correct? Correct?
A. I said "no." Correct.
Q. You're not aware of any evidence that women who use external genital talc have increased risk of vaginal cancer, correct?
A. I do not.
Q. And I believe with Mr. --
A. James.
Q. -- Mr. Scott James you talked about no -- awareness of no increase in cervical cancer or uterine cancer in talc users, correct?
A. You are correct.
Q. And also, talc applied to the external genital area would come into contact with the rectal area, correct?
MS. O'DELL: Objection.
A. It -- yes.
Q. (BY MR. KLATT) Are you aware of any evidence that women who use talc in the genital area have an increased risk of rectal cancer?
A. I do not have any evidence to that effect.

Q. You're aware that Dr. Saed has just started writing about talc in relation to ovarian cancer since he's become a retained litigation expert by the plaintiffs, right?
MS. O'DELL: Objection to form.
A. I can't tell you the exact first time he did an experiment or published a result with that. I can't -- I . . .
Q. (BY MR. KLATT) You're not aware of Dr. Saed making any sort of connection between talc and ovarian cancer before you got involved in this litigation, correct?
A. I -- I'm not aware of that.
Q. IARC has not said that any of the heavy metals you cite in your report increase the risk of ovarian cancer, correct?
A. They have called them Class 1 carcinogens, and there's been no association with ovarian cancer made in their report.
Q. And you're not aware of any evidence that women who use talc-based body powder products have increased blood or tissue levels of cadmium, cobalt, chromium, or nickel, compared to women who never use those products --

A. I know no evidence --
Q. -- correct --
MS. O'DELL: Objection; form.
A. -- to that effect.
MS. O'DELL: Excuse me. Objection to form.
Q. (BY MR. KLATT) Is that correct?
A. I know no evidence to that effect.
Q. And finally, Doctor, and I think it's very admirable what you're currently doing with the women who are in hospice care for ovarian cancer.
When you interact with these women, you interact not only with the women but with their family and friends as well, correct?
A. Absolutely.
Q. Now, have you ever told any of their family or friends that they shouldn't use talc --
MS. O'DELL: Objection to form.
Q. (BY MR. KLATT) -- in the genital area?
A. I think it would be quite inappropriate to have that conversation at that time.
Q. Well, these are women -- these are mothers, sisters, daughters, and female friends of these women who are dying with ovarian cancer,

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correct?
MS. O'DELL: Objection to form.
A. I have never told them -- counseled a family member or a friend or a child of a dying ovarian cancer patient about genital talc use.
Q. (BY MR. KLATT) You haven't said a word about it right up until as we sit here today; is that correct?
MS. O'DELL: Objection to form.
A. Correct.
MR. KLATT: Thank you. That's all I have.
MR. JAMES: I don't have any further questions.
MS. O'DELL: Okay.
FURTHER EXAMINATION
BY MS. O'DELL:
Q. I have -- have -- let me just ask one question.
In the situation when you're counseling a family of a dying patient, would it be inappropriate to have a discussion that Mr. Klatt suggested?
A. I feel it would be.

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MS. O'DELL: Okay. I have no further questions.
FURTHER EXAMINATION
BY MR. KLATT:
Q. Well, let me ask one more question about that.
Do you ever care for women who are dying from ovarian cancer due to BRCA1 or BRCA2 mutations?
MS. O'DELL: Object to the form.
A. I -- in my life? Yes.
Q. (BY MR. KLATT) And you would certainly counsel those women to have their female mothers, sisters, daughters, and friends -- well, mothers, sisters, and daughters tested for those mutations, correct, because you'd want them to take steps to potentially avoid the risk of ovarian cancer.
A. Correct.
MS. O'DELL: Objection.
MR. KLATT: Thank you.
MS. O'DELL: I have nothing further.
THE VIDEOGRAPHER: This concludes the deposition of Ellen Blair Smith, M.D. Going off the record. The time is 9:22 p m.

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MR. JAMES: Thank you, Dr. Smith.
(Discussion off the record.)
THE COURT REPORTER: Leigh, would you like the witness to read and sign?
MS. O'DELL: Yes, I would.
THE COURT REPORTER: Would you like it to go to you or directly to the witness?
MS. O'DELL: To me.

(Deposition concluded at 9:23 p.m., January 9, 2019.)

Page 381

CHANGES AND SIGNATURE
WITNESS NAME: ELLEN BLAIR SMITH, M D
DATE: JANUARY 9, 2019
PAGE/LINE CHANGE REASON
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I, ELLEN BLAIR SMITH, M D., have read the foregoing deposition and hereby affix my signature that same is true and correct, except as noted above.

____
ELLEN BLAIR SMITH, M.D.

THE STATE OF __________)

COUNTY OF ____________)

Before me, __________________________, on this day personally appeared ELLEN BLAIR SMITH, M.D., known to me (or proved to me under oath or through __________________________) (description of identity card or other document) to be the person whose name is subscribed to the foregoing instrument and acknowledged to me that they executed the same for the purposes and consideration therein expressed.

Given under my hand and seal of office this __________ day of _______________________, 2019.

____
NOTARY PUBLIC IN AND FOR
THE STATE OF ______________

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON)
TALCUM POWDER PRODUCTS)
MARKETING, SALES)
PRACTICES, AND PRODUCTS) MDL NO:
LIABILITY LITIGATION) 16-2738 (FLW)(LHG)
)
THIS DOCUMENT RELATES TO)
ALL CASES)

REPORTER'S CERTIFICATE

\---
DEPOSITION OF ELLEN BLAIR SMITH, M.D.
TAKEN JANUARY 9, 2019
\---

I, Karen L. D. Schoeve, Registered Diplomate Reporter, Certified Realtime Reporter, and Realtime Systems Administrator, residing in the State of Texas, do hereby certify that the foregoing proceedings were reported by me and that the foregoing transcript constitutes a full, true, and correct transcription of my stenographic notes, to the best of my ability and hereby certify to the

following:

That the witness, ELLEN BLAIR SMITH, M.D., was duly sworn by the officer and that the transcript of the oral deposition is a true record of the testimony given by the witness;

That the original deposition was delivered to SCOTT A. JAMES, custodial attorney;

That a copy of this certificate was served on all parties and/or the witness shown herein on __________________________.

I further certify that pursuant to FRCP No. 30(f)(i) that the signature of the deponent was requested by the deponent or a party before the completion of the deposition and the signature is to be returned within 30 days from date of receipt of the transcript.

If returned, the attached Changes and Signature Page contains any changes and the reasons therefor.

That pursuant to information given to the deposition officer at the time said testimony was taken, the following includes counsel for all parties of record:

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I further certify that I am neither counsel for, related to, nor employed by any of the parties in the action in which this proceeding was taken, and further that I am not financially or otherwise interested in the outcome of the action

(Continued on following page)

Subscribed and sworn to on this the 11th day of January, 2019.

____

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B

Exhibit 17

ENVIRONMENTAL RESEARCH 40, 247–250 (1986)

The Demonstration of the Migration of Talc from the Vagina and Posterior Uterus to the Ovary in the Rat

W. J. HENDERSON, T. C. HAMILTON,[1] M. S. BAYLIS, C. G. PIERREPOINT, AND K. GRIFFITHS

Tenovus Institute for Cancer Research, University of Wales College of Medicine, The Heath, Cardiff CF4 4XX, Wales

Received May 15, 1984

Talc particles placed in both the uterine cavity and the vagina of the rat were shown to migrate to the ovary and become localized within its substance. © 1986 Academic Press, Inc.

INTRODUCTION

The presence of talc particles deeply embedded in ovarian and cervical benign and malignant tissue was reported by this Institute (Henderson *et al.*, 1971). Positive identification of the particles was achieved (Griffiths *et al.*, 1973) by replicating the surface morphology of tissue sections (Henderson, 1969) and analyzing the X-ray emission spectra of extracted foreign material with an electron microscope microanalyzer (EMMA, A. E. I. Harlow, England).

Direct communication between the external environment and the peritoneal cavity exists in the female via her genital tract. It has been demonstrated that the injection of a suspension of talc beneath the bursa of the rat ovary was followed by the development of large ovarian bursal cysts, with associated epithelial changes not inconsistent with the histological picture of premalignancy (Hamilton *et al.*, 1984). It was, therefore, of interest to see whether talc placed in the lower part of the female genital tract of the rat would migrate anteriorly to the ovary.

MATERIALS AND METHODS

In a pilot study eight female exbreeder Sprague–Dawley rats 7.5 months old were used. Under light ether anesthesia a speculum of an auroscope with the lens removed was introduced into the vagina and the cervical os illuminated. A Portex catheter (o.d. 0.75 mm) was passed a distance of approximately 2.5 cm into the cervical canal from the vagina introitus and a suspension of talc (100 mg/ml) in phosphate-buffered saline (PBS) introduced (vol 250 μl). The animals were divided into two groups of four. Group I was sacrificed 5 days following intrauterine instillation of the talc suspension and their ovaries were removed. The animals in Group II received further uterine instillations 6 and 15 days after the initial treatment. On Day 20, two rats from this group were killed and their ovaries removed. The remaining two rats received further treatments 22 and 30 days after their initial treatment and were sacrificed on Day 49.

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0013-9351/86 $3.00

The ovaries from each animal were combined and subjected to an ashing procedure as described previously (Henderson *et al.*, 1978). Essentially this process removes organic matter by heating the organs to 550°C in the incineration chamber of a horizontal tubular muffle furnace in a stream of oxygen (250 ml/min/500 mg wet wt for 5 hr). The ashed material was then suspended in distilled water (50 μl). Aliquots (10 μl) were pipeted onto carbon-coated electron microscope grids and the water was evaporated. A further carbon coat was applied *in vacuo* to stabilize any particles and to dissipate heat and electrostatic charge generated by the concentrated electron beam prior to examination with the EMMA.

Twelve Sprague–Dawley exbreeder rats of a similar age to those used in the experiment described above were divided into two groups of six. Group I animals were firmly held and the louver of a 1-ml disposable microjet 501 TB syringe was introduced into the vaginal orifices and 250 μl of a suspension of talc (100 mg/ml) in PBS was deposited into the vaginas. The animals in Group II were treated similarly except that 250 μl of PBS was substituted for the talc suspension. Two animals from each group were sacrificed 24 hr, 48 hr, and 4 days, respectively, following initial treatment. Their ovaries were removed and treated similarly to those described in the first experiment.

RESULTS

Particles of talc were identified in the ovaries of all the animals that received intrauterine talc and in the two animals that received intravaginal talc killed after 4 days (Fig. 1a). X-Ray analysis (Fig. 1b) confirmed the chemical constitution of talc. No talc could be demonstrated in the group of rats that had received PBS intravaginally or in those animals with intravaginal talc killed after 24 and 48 hr.

DISCUSSION

Birefringent particles were first noted to be present in human ovarian carcinomas by Graham and Graham (1967) who postulated that these particles might be asbestos. Subsequent work at this Institute identified talc in ovarian cancer tissue but not asbestos (Henderson *et al.*, 1971; Griffiths *et al.*, 1973). The ease of migration of particulate material from the vagina to the peritoneal cavity (Venter and Iturralde, 1979; Iturralde and Venter, 1981) has been established.

The physiological mechanisms associated with translocation of particulate material within the genital tract are unknown but are probably operative in most mammalian species. The chemical nature of the particulate would not appear to alter its ability to be transported through the genital tract and does not elicit any selective mechanisms. Indeed it is accepted that retrograde flow of menstrual products into the peritoneal cavity via the Fallopian tubes is not an uncommon finding by laparoscopy at the time of menstruation. The rhythmic muscular contractions of the uterus that occur spontaneously and the illicit currents established by the epithelial cells of the genital tract may contribute to the translocation process.

Talc is widely used in the cosmetic and pharmaceutical industry and has been associated with the use of certain forms of barrier contraceptives. Many women apply talc to their perinea and some to their sanitary ware (Cramer *et al.*, 1982).

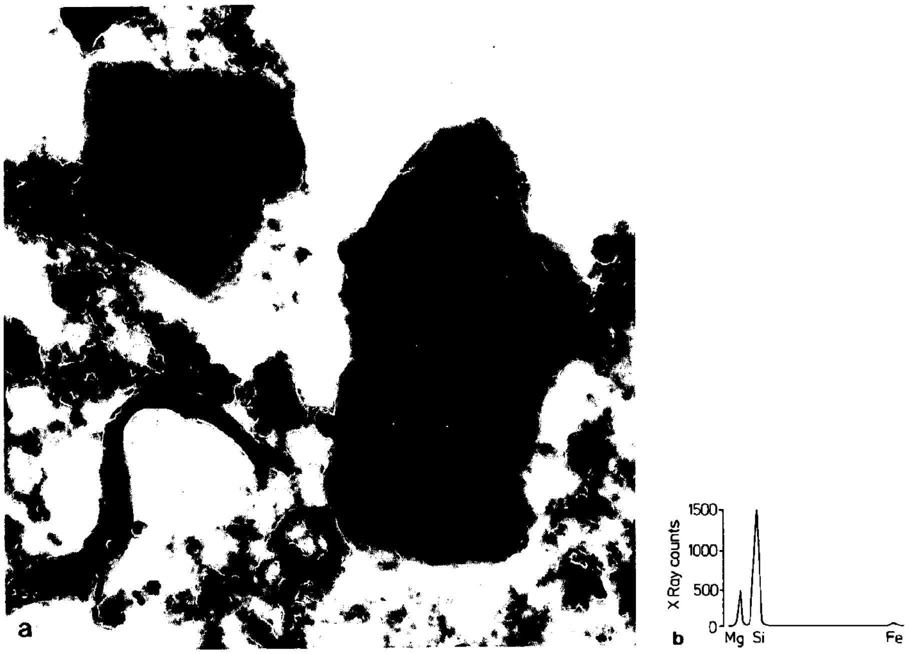

FIG. 1. (a) Particles of talc recovered from the ovary by oxygen ashing following instillation of a suspension of talc into the posterior genital tract of a rat (10,000×). (b) Spectral analysis of the particles showing the 3:1 ratio of silicon to magnesium characteristic of talc.

The association of talc with formation of granulomata is well documented (Lichtman *et al.*, 1946) and it may be speculated that disruption of normal ovarian stromal structure may lead to disturbances in steroid hormone metabolism.

Carcinogenic activity of talc has not been established although its ubiquitous presence in the environment and its elemental similarity to asbestos has brought it under suspicion (Longo and Young, 1979). However, it has been found in both normal and malignant tissue and its precise role remains unclear, although Cramer *et al.* (1982) suggested that a relationship between increased incidence of ovarian cancer and the use of talc existed. A long latent period from the initial exposure to talc to the induction of malignant change has been postulated (Katsnelson and Mokronosova, 1979), but until a greater understanding of the biological properties of talc is achieved further speculation is unjustified at this time.

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Exhibit 18

Journal of The American College of Obstetricians and Gynecologists

Obstetrics and Gynecology

Volume 64 *August 1984* *Number 2*

Retrograde Menstruation in Healthy Women and in Patients With Endometriosis

JOUKO HALME, MD, PhD, MARY G. HAMMOND, MD, JAROSLAV F. HULKA, MD, SHAILAJA G. RAJ, MD, AND LUTHER M. TALBERT, MD

Blood was found in the peritoneal fluid in 90% of women with patent tubes at laparoscopy during perimenstrual time. If the fallopian tubes were occluded, then only 15% of patients had evidence of blood in the pelvis. Also, 90% of patients with endometriosis and eight of nine women on oral contraceptives had bloody fluid during the menstrual period. The present observations indicate that retrograde menstruation through the fallopian tubes into the peritoneal cavity is a very common physiologic event in all menstruating women with patent tubes. ***(Obstet Gynecol 64:151, 1984)***

In 1927 Sampson proposed that endometriosis was due to implantation of endometrial cells during retrograde menstruation.[1] During his lifetime, most of the opponents of this theory dismissed it mainly on the basis that retrograde menstruation, although occasionally noted to occur, was a relatively rare phenomenon.[2,3] Therefore, it would not explain the development of a common clinical entity such as endometriosis. Since that time, the frequency of retrograde menstruation has been debated.

From the Division of Reproductive Endocrinology and Fertility, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.

Supported in part by the Kenneth D. Dickinson Fund.

No systematic studies documenting the incidence of retrograde menstruation have been published in spite of the fact that millions of women have undergone laparotomy or laparoscopy, making possible direct observations of pelvic structures. Recently, however, Blumenkrantz et al[4] reported that nine of 11 menstruating women undergoing peritoneal dialysis had blood present regularly in the dialysate during the time of their period and in this way documented retrograde menstruation. They also suggested that this event was a rather common phenomenon, and not limited to women with renal failure. In addition, a study from the authors' institution reported that of 80 peritoneal fluid samples, all four obtained during menses were bloody.[5]

Based on laparoscopy of 323 women, the current study presents further evidence suggesting that retrograde menstruation occurs in most menstruating women who have open fallopian tubes.

Material and Methods

Between July 1980 and September 1983, 331 pelvic fluid samples were obtained from patients undergoing laparoscopy at The North Carolina Memorial Hospital. Of

181 patients with patent tubes and normal pelves, 78 underwent laparoscopy for bilateral tubal ligation, and 103 were undergoing diagnostic laparoscopy for evaluation of infertility or chronic pelvic pain. Of 40 patients with occluded fallopian tubes, 16 had distal blockage, two had proximal blockage, and 22 had proximal occlusion as a result of previous tubal ligation. Eighty-one patients were noted to have mild to moderate endometriosis.

Peritoneal fluid was aspirated with an 18-gauge Silastic catheter through the operative channel of the laparoscope and collected into a heparin-containing test tube. The color of the fluid, when in the tube, was recorded either as straw, pink, or bloody. Upon reviewing the records of these patients, the date of the last normal menses in 302 patients, and observations on the fluid samples were available. In addition, 21 women who were on oral contraceptives were identified.

Because only visual documentation of the color of the fluid was available for all samples, an experiment was set up to test the accuracy of this technique in assessment of the presence of blood. A series of 30 tubes containing ten different concentrations of red blood cells (ranging from hematocrit of 0 to 10) in peritoneal fluid was constructed. The tubes were shown in a random order to each of the nine persons involved in classifying these fluids into one of the three color categories. The color was judged as straw when hematocrit was less than 0.5 ± 0.2% (SD) and bloody when hematocrit was higher than 3.2 ± 2.0%. Between these values, the color was judged to be pink. The level of agreement between different individuals and by each individual between two testing occasions (the coefficient κ) was determined according to Cohen[6]

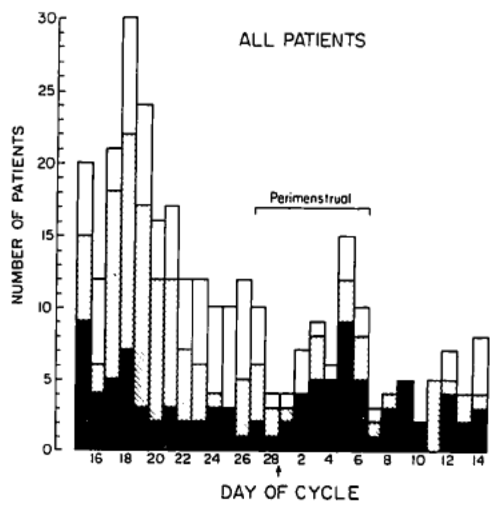

Figure 1. Appearance of all 302 peritoneal fluid samples obtained during laparoscopy. Solid bars = bloody; shaded bars = pink; open bars = straw.

Table 1. Appearance of Peritoneal Fluid Samples Obtained on Nonmenstrual Days 7 to 26

	No endometriosis		
	Open tubes	Closed tubes	Endometriosis
Straw	54	11	14
Pink or bloody	85	16	57
Total	139	27	71

and Fleiss.[7] Values of κ ranged from 0.39 to 1.0 between pairs of individuals and from 0.52 to 1.0 between the two testings.

Observations by Blumenkrantz et al[4] suggested that the presence of blood in the peritoneal dialysates usually preceded the beginning of menstrual flow by one to two days. Therefore, the patients in this series were divided in two groups: 1) perimenstrual, if they underwent laparoscopy on days one to six or 27 to 30 of their cycle, and 2) nonmenstrual, if laparoscopy was performed between days 7 to 26 of the cycle.

Statistical analysis of the data was performed by using the χ^2 statistic for 2 × 2 contingency tables constructed for pairs of variables and normal approximation for the binomial distribution.[8]

Results

Figure 1 presents the noted color of each of the 302 fluid samples in perimenstrual and nonmenstrual phases of the cycle. It is obvious from the graph that there is an increased amount of blood in the pelvic cavity around the time of menses and also immediately after ovulation with clearance of that blood over the next five to six days.

As indicated in Table 1, a total of 237 fluid samples were obtained in the nonmenstrual phase. Overall one-third of these fluids were straw, and the other two-thirds contained an appreciable amount of red blood cells (either pink or bloody). In normal women with open fallopian tubes, 61.1% of fluids were either pink or bloody as compared with 60% in women with occluded tubes, suggesting that tubal patency is not an important factor for the presence of blood in the peritoneal cavity during the nonmenstrual phase of the

Table 2. Appearance of Peritoneal Fluid Samples Obtained on Perimenstrual Days 1 to 6 and 27 to 30

	No endometriosis		
	Open tubes	Closed tubes	Endometriosis
Straw	4	11	1
Pink or bloody	38	2	9
Total	42	13	10

normal cycle. In the 12 women on oral contraceptives who underwent laparoscopy during this phase of the cycle, six had pink fluid in the cul-de-sac. In patients with endometriosis, blood was detected significantly more often ($P \leq .005$) than in other women with patent tubes in the nonmenstrual phase.

Table 2 presents corresponding data for fluid samples obtained during the perimenstrual phase of the cycle. Of 52 samples from women with patent fallopian tubes, 47 (90.4%) had an appreciable amount of red blood cells; 70% of these were grossly bloody. This is significantly different ($P \leq .001$) than the corresponding percentage in nonmenstrual samples. In the nine women on oral contraceptives who underwent laparoscopy in the perimenstrual phase, eight had bloody fluid. Only two of 13 (15.4%) patients with occluded tubes had red blood cells (one pink and one bloody sample) in the peritoneal fluid. This frequency is significantly lower ($P \leq .005$) than in women with open tubes. These figures clearly indicate that during the perimenstrual phase, the peritoneal fluid in almost all women, including those taking oral contraceptives, contains blood and that the fallopian tubes play an important role as conduits for menstrual blood.

Discussion

The important clinical observations by Blumenkrantz et al[4] in women undergoing peritoneal dialysis indicated that bleeding into the dialysate usually was detectable one to two days before the menstrual period and during the menses. The recognition of this phenomenon prompted the authors to include the patients undergoing laparoscopy on these premenstrual days in the perimenstrual group rather than in the nonmenstrual group. The results of this study clearly indicate that during this perimenstrual time of the cycle, over 90% of normal and infertile women have blood in their peritoneal fluid. If the tubes are occluded, there is no correlation between the perimenstrual phase and the presence of blood in the pelvis. This indicates that the fallopian tubes are the major conduit for blood entering the peritoneal compartment at the time of menses.

The use of oral contraceptives has been advocated as a possible means of protection from endometriosis,[5,9] but it may be inferred from the present data that if used noncontinuously, allowing menstruation to occur, retrograde menstruation will also occur, as these women consistently had blood in the pelvic fluid at this time. To prevent this, an uninterrupted mode of administration may be necessary.

Many studies have demonstrated that various volumes of peritoneal fluid are found in the female pelvis during laparoscopy.[5,10,11] This fluid in the pelvis often seems to contain blood.[12,13] In 69% of all patients in this series, an appreciable amount of blood was detected. Sources of this blood include the abdominal wall stab wound(s) and severed vessels in omentum or adhesions in the pelvis. This contamination with fresh blood is always variably present in addition to blood derived from natural, physiologic phenomena like ovulation, and eventually, retrograde menstruation. It is not possible to accurately assess the impact of this contamination, but it may be safe to assume that this iatrogenic hemorrhage occurs at random and is not dependent on any particular time of the cycle. Furthermore, observation (not shown) that even grossly bloody peritoneal fluid samples obtained during menses did not contain appreciable numbers of granulocytes suggests that the blood did not result from an immediate hemorrhage to the pelvic compartment.

Sampson[1] originally suggested that retrograde menstruation provides a mechanism by which endometrial cells can implant on peritoneal surfaces in women with endometriosis. Because the great majority of the authors' patients either with or without endometriosis showed evidence of retrograde menstruation, it cannot explain why only some women have developed the disease. Other factors, either hormonal or immunologic, will apparently determine whether or not ectopic implantation can take place. Koninckx et al[14,15] demonstrated a high incidence of luteinized unruptured follicle syndrome in women with endometriosis, and also a low, late luteal phase progesterone/estrogen ratio of peritoneal fluid in this syndrome. They hypothesized that this local hormonal imbalance may be critical in allowing endometrial cells, if present in the peritoneal compartment, to implant on the peritoneum. The results of the present study provide direct evidence that cells originating from the uterine cavity indeed are present in the pelvis in the late luteal phase preceding menses, and this theory may hold if peritoneal fluid hormone levels are abnormal. However, a recent study[16] found no difference in progesterone and estrogen levels during this time in the fluid of women with or without endometriosis. However, several sources[17,18] suggest that abnormal immunologic defense mechanisms may be operative in women with endometriosis, and this can explain the occurrence of ectopic implantation of endometrium. More detailed comparative information on both hormonal and immunologic function in a sizeable population of both normal women and patients with endometriosis is clearly warranted.

Studies on peritoneal macrophages[5,19] have demonstrated that samples taken at menstruation usually have the highest concentrations of these cells, the majority of which are recent arrivals. It was suggested that this influx of phagocytic macrophages to the pelvis

is a response to retrograde menstruation. The present results clearly support this idea, and it remains to be seen whether or not the nucleated cellular components of menstrual detritus are also regularly transported through the fallopian tubes. Studies are in progress in The North Carolina Memorial Hospital to detect the presence of either epithelial or stromal cells of endometrial origin in peritoneal fluid.

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Exhibit 19

high. The few cases in which progestin therapy resulted in improvement of symptoms and relief of obstruction suggest that there may be a place for selective medical management. Patients who are young and wish to preserve their childbearing capacity may be considered initially for such treatment. Fertility potential is probably poor in this group of patients because of the extent of their pelvic endometriosis. Patients considered for medical management should be informed of the risks of permanent renal damage and treated with close surveillance of renal function.

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Retrograde Menstruation in Women Undergoing Chronic Peritoneal Dialysis

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Blood in the peritoneal dialysis catheter just before menstruation was regularly observed in 9 of 11 premenopausal women maintained on peritoneal dialysis for end-stage renal failure. Peritoneal bleeding at other times during the menstrual cycle was not seen in any of these patients. Likewise, peritoneal bleeding in men or nonmenstruating women on chronic peritoneal dialysis was exceedingly rare, was not periodic, and usually was due to recognizable causes. These observations suggest that retrograde menstrual bleeding into the peritoneal cavity is the rule rather than the exception in women on peritoneal dialysis and possibly in all menstruating women. Implications of this observation for the pathogenesis of endometriosis and dysmenorrhea are discussed. *(Obstet Gynecol 57:667, 1981)*

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The incidence of retrograde menstruation and its consequences have been the topic of extensive debate. Sampson[1] suggested that retrograde menstruation is the cause of external endometriosis, noting that blood was frequently observed escaping from the ostea of the fallopian tubes in menstruating women who were undergoing pelvic surgery. Novak questioned this theory on the grounds that retrograde menstruation was rare as compared to the observed frequency of endometriosis.[2,3] Watkins reported bloody fluid containing endometrial cells aspirating from the cul-de-sac during menstruation.[4] Other reports note the occasional appearance of blood in the pelvic cavity at the time of culdoscopy or pelvic surgery when performed during menstruation.[5-9]

This communication describes observations in menstruating women on maintenance peritoneal dialysis who were noted to have blood in the peritoneal catheters or in the effluent dialysate coincident with menstruation.

Patients and Materials

The development of implantable Silastic catheters has made it possible to maintain selected patients with end-stage renal failure alive and well for extended periods by means of peritoneal dialysis.[10] A silicone rubber catheter is implanted through the abdominal wall with its intraabdominal section usually lying in the pelvic cavity. During intermittent peritoneal dialysis,

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sterile dialysate is pumped through the catheter into the peritoneal cavity, where it remains for a specified dwell period; then it is drained and replaced by fresh dialysate. This cycle is generally repeated every 30 minutes during a 12-hour overnight treatment period. Most patients require 3 treatments per week. The transparent external catheter segment is closed between treatments by a disposable rubber cap and represents a fluid-filled extension of the peritoneal cavity. The character of the peritoneal fluid in the catheter can be observed prior to dialysis or in the effluent of the initial dialysis cycle. Heparin was not routinely added to the dialysate in any of these patients. Bleeding into the peritoneal cavity is usually readily detectable by the presence of a red thread of sedimented red blood cells within the transparent external Silastic catheter segment. Occasionally blood is not apparent until the first exchange of dialysate is being drained.

The records of all women between the ages of 15 and 50 who were maintained on peritoneal dialysis were reviewed. A total of 11 women with a history of menstrual bleeding after initiation of maintenance peritoneal dialysis was identified (Table 1). All patients were interviewed to obtain a detailed menstrual history to supplement the official record. At the time of data collection 5 of the women were no longer on peritoneal dialysis; 3 had undergone successful renal transplantation and 2 had been switched to hemodialysis. At the time of the interview, patients 10 and 11 had only a vague recollection of their menstrual history.

The 11 patients had a mean age of 38.8 years (range, 15 to 44 years); all had been on maintenance home peritoneal dialysis and were followed at the University of Washington or the Northwest Kidney Center in Seattle. Uremic symptomatology was controlled in all these patients and they were as well as comparable patients undergoing hemodialysis. Eight of the 11 women had experienced cessation of menstruation prior to dialysis; 1 patient had primary amenorrhea, 4 were nulliparous, and 7 were multiparous.

Three of the 11 women who were on maintenance peritoneal dialysis at the time of the survey had peritoneal fluid collected on several occasions in the course of their menstrual cycles and when blood was in evidence. The fluid specimens were aspirated aseptically from the peritoneal catheter and placed into sterile glass flasks, which were sent immediately or after overnight refrigeration to the cytology laboratory for processing.

Results

Eight of 11 women listed in Table 1 developed secondary amenorrhea coincident with the development of chronic renal failure. All 8 resumed menstruation after maintenance peritoneal dialysis was instituted. The mean time interval from the beginning of dialysis to resumption of menstruation was 7.7 months. Menstruation had not ceased in patients 6 and 11. Patient 7 had primary amenorrhea. Of the 9 patients who experienced resumption of menstruation or menarche after initiation of peritoneal dialysis, 5 were noted to have regular menses and 6 had irregular menses. With the exception of patients 10 and 11, both of whom had only 2 very scanty periods, all patients were noted to have small amounts of blood in their peritoneal catheter and/or in the effluent dialysate coincident with

Table 1. Menstrual History of Women Who Had Noted Blood in Catheter and/or Effluent Dialysate While Undergoing Maintenance Peritoneal Dialysis

Patient	Age at onset of dialysis	Cessation of menstruation prior to to dialysis	Months of dialysis until resumption of menstruation	Menstruation		Blood in catheter and/or effluent dialysate
				Regularity	Flow	
1	17	Yes	3	Regular	Moderate	Yes
2	21	Yes	6	Regular	Moderate	Yes
3	40	Yes*	5	Irregular	Heavy	Yes
4	40	Yes	5	Irregular	Scanty	Yes
5	36	Yes	12	Regular	Moderate	Yes
6	34	No	—	Irregular	Moderate	Yes
7	15	—†	32	Regular	Scanty	Yes
8	44	Yes	2	Regular	Moderate	Yes
9	25	Yes	3	Irregular	Heavy	Yes
10	40	Yes	—	Irregular	Scanty‡	No
11	27	No	—	Irregular	Scanty‡	No

* Contraceptive injection.
† Primary amenorrhea.
‡ Only 2 periods.

the time of menstruation. Blood always appeared in the dialysate or in the catheter a few days prior to the onset of vaginal bleeding, and it usually persisted during the first day of menstrual flow. Patient 6 consistently noted blood in the peritoneal catheter 4 days before the onset of menstruation. In several of the patients the appearance of blood in the dialysate was the first sign of the return of menses after secondary amenorrhea. In patient 7, menarche was noted at the age of 19 by the appearance of peritoneal blood. This patient had started dialysis at the age of 15, at which time she had no secondary sexual development.

Six of the 11 patients (patients 1 through 5 and 7) eventually underwent laparotomy for nephrectomy and/or splenectomy prior to renal transplantation. In none of these patients was endometriosis noted at the time of abdominal surgery. Menstrual blood loss did not have a significant effect on hematocrit levels in these women, none of whom required blood transfusions once stabilized on peritoneal dialysis. Although numerous attempts were made in 3 of the patients to identify endometrial or tubular epithelial cells in the peritoneal effluent or aspirate, unequivocal evidence for such cells in any of the specimens was not obtained.

Discussion

With advancing renal failure, as with other debilitating diseases, secondary amenorrhea often develops. Hemodialysis therapy has been reported to be associated with resumption of menstrual periods in some patients, menorrhagia in others, and persistent amenorrhea in a third group.[11,12]

In this series 11 women under the age of 45 who were treated with chronic peritoneal dialysis and who continued or resumed menstrual periods are reported. The presence of an implanted intraabdominal catheter afforded an opportunity to observe the character of peritoneal fluid over months or years. When patient 1 first noted blood in the effluent dialysate she was alarmed, and her physician was at a loss to explain the phenomenon. This first episode was not associated with vaginal bleeding. In subsequent months, blood staining of her peritoneal fluid occurred at regular intervals in association with vaginal bleeding. In the course of subsequent years the same phenomenon was observed in all women who resumed menstrual cycles while undergoing peritoneal dialysis. The 2 exceptions were patients 10 and 11, each of whom had only 2 periods with very scanty flow after initiation of dialysis. As both had undergone dialysis at home and neither was a good observer, it is conceivable that small amounts of peritoneal blood may have escaped their attention. Resumption of periods was often indicated by blood in the effluent dialysate before vaginal bleeding occurred.[13] None of the women had a history of dysmenorrhea or showed evidence suggestive of pelvic endometriosis; this was verified in 6 of the 11 women during pretransplant laparotomy. In men and nonmenstruating women, blood in the peritoneal catheter or effluent dialysis is exceedingly rare and usually can be explained by a detectable anomaly such as peritonitis, intraabdominal malignancy, recent abdominal surgery, or tissue herniation into the implanted catheter with subsequent hemorrhage.

The authors think it highly unlikely that hormonal alterations or anatomic abnormalities associated with chronic renal failure or dialysis explain the high frequency and regular occurrence of blood in the peritoneal cavity coincident with the time of menstruation. Likewise, it would appear most unusual for mechanical irritation by the peritoneal catheter to occur exclusively in menstruating women and in association with menstrual flow. These observations suggest strongly that retrograde bleeding regularly occurs with menstruation in most if not all women on peritoneal dialysis and quite possibly in most menstruating women in the general population.

The current emphasis on prostaglandin as a possible cause of dysmenorrhea notwithstanding,[14] it remains intriguing to speculate on the role that retrograde menstruation may play in the pathogenesis of dysmenorrhea. If retrograde menstrual bleeding is the rule rather than the exception, then bleeding must be asymptomatic in most women as it was in these patients, none of whom has a history of dysmenorrhea. As most women do not experience dysmenorrhea, this lack of pain may be a reflection of low peritoneal reactivity to irritation by blood or other irritants. Variability in the pain threshold to intraabdominal blood is well known to surgeons confronted with hemoperitoneum and to gynecologists treating endometrial disease. Similarly, the present authors and others with extensive peritoneal dialysis experience have observed remarkable individual differences in abdominal pain response to acid peritoneal dialysis solutions. Thus, both the amount of blood spill and individual reactivity may be important modulating factors in the causation of dysmenorrhea. In this context, it may also be of interest to recall that retrograde bleeding usually occurred 1 or several days prior to the onset of vaginal bleeding and ceased when vaginal flow commenced, a pattern analogous to that of the pain prevalent in dysmenorrhea, especially in nulliparous women.

Cervical or other obstruction to free flow during the initial phase of menstruation may contribute to or aggravate abdominal spillage of blood and may help ex-

plain premenstrual pelvic congestion and its relief by establishment of cervical blood flow, especially in nulliparous women. Obstruction to free flow also appears to be associated with early establishment of pelvic endometriosis in teenagers,[15,16] an age group not normally affected by this disease.

The observation of frequent, perhaps regular retrograde menstruation in most women tends to support Sampson's theory of retrograde menstrual bleeding as the most likely and most frequent cause of pelvic endometriosis. Watkins[4] had rejected this notion because he believed retrograde bleeding was too infrequent to account for the incidence of endometriosis. However, it was Watkins who reported endometrial cells in the cul-de-sac of menstruating women, a finding supported by other workers in this field, most recently by Gahl,[17] who observed tubal epithelial cells in the peritoneal effluent of women undergoing peritoneal dialysis. Although retrograde bleeding does not explain why only some women develop endometriosis, these findings rebuke Watkins' objections to the spill-implantation theory of endometriosis.

Addendum

Since the compilation of the data for this report, the authors have treated additional patients who menstruated while being maintained on peritoneal dialysis. All showed evidence of retrograde bleeding in the catheters or in the initial peritoneal effluent, except 1 patient who had undergone tubal ligation.

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Fatal case of cytomegalovirus pneumonitis in a postpartum woman

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This is the first reported fatal case of cytomegalic inclusion disease in a pregnant woman. The 28-year-old woman died after cesarean section for cephalopelvic disproportion. The diagnosis of cytomegalic inclusion disease was made at autopsy by finding enlarged pneumocytes with typical intranuclear inclusions, positive direct immunofluorescence on the lung tissue with antibody specific for cytomegalovirus, and retrospective serologic titers of 1:64 for the virus. The time of the infection is unclear, but the absence of infection in the newborn may suggest an onset late in pregnancy; there was no evidence of disease before labor and cesarean section. *(Obstet Gynecol 57:670, 1981)*

Exhibit 20

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Retrograde migration of glove powder in the human female genital tract

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BACKGROUND: This study in humans was undertaken to evaluate earlier results from animal research showing a retrograde migration of glove powder from the vagina into the intra-abdominal cavity. METHODS: One study group was gynaecologically examined with powdered gloves the day before an abdominal hysterectomy and another group 4 days pre-operatively. There were two control groups similarly examined with powder-free gloves. Cell smears were taken from the peritoneal fluid and during the operation further smears were taken from the Fallopian tubes, uterine cavity and cervical canal. RESULTS: Statistically significant differences were found for large starch particles at all locations between the study and control groups examined 1 day pre-operatively. Considering small starch particles, there were significant differences in cervix ($P < 0.001$), uterus ($P < 0.01$) and the Fallopian tubes ($P < 0.01$). The combined results also show significant differences between both large and small starch particles in cervix, uterus and the Fallopian tubes. There were also differences between the study and control groups examined 4 days pre-operatively, but these were not statistically significant except for small and large starch particles in uterus ($P < 0.01$, $P < 0.05$) and cervix ($P < 0.05$, $P < 0.05$). CONCLUSIONS: This study has pointed out a retrograde migration of starch also in humans after a gynaecological examination with powdered gloves. Consequently, powder or any other potentially harmful substance that can migrate from the vagina should be avoided.

Key words: female/gloves/retrograde migration/starch particles/vaginal examination

Introduction

Earlier case reports suggest that intra-abdominal granulomas or adhesions due to starch particles were caused by starch powder used on gloves during vaginal examination. An initial indication of retrograde flow through the Fallopian tubes was the finding of intraperitoneal starch granulomas (Paine and Smith, 1957). Later the first case of starch peritonitis in a patient without previous surgery was reported (Saxen *et al*., 1963). A recent investigation detected talcum particles on the ovaries in women who had used perineal talc applications (Heller *et al*., 1996). In contrast, tubal ligation prevents the access of mediators that reach the peritoneal cavity through the Fallopian tubes (Ylikorkala, 2001).

Powder-free gloves have been available for 20 years, but starch-powdered gloves are still available and in use (Sjösten *et al*., 1999).

It is well documented that starch-powdered gloves are not appropriate for abdominal surgery (Ellis, 1990; Holmdahl *et al*., 1994), and intraperitoneally, starch particles can initiate inflammatory reaction and the formation of adhesions (Edelstam *et al*., 1992; diZerega, 1994), although the mechanism by which starch increases the propensity of tissues to form adhesions is not known. Reduced peritoneal fibrinolysis and activation of leukocytes by particulate starch granules have been suggested as possible mechanisms. Activated leukocytes, particularly macrophages, produce supernormal amounts of oxygen-free radicals, prostaglandin E_2, thromboxane B_2 and various cytokines (Osman and Jensen, 1999). Starch particles also increase the eicosanoid production which may contribute to the inflammatory or immune reactions and development of adhesions (Chegini and Rong, 1999). If already injured mesotelial surface of the peritoneum is exposed to starch, more dense adhesions are created compared to the effect of peritoneal trauma or starch separately. Application of glove powder on minimally or severely traumatized peritoneum facilitates tumour cell adhesion and growth alone (van den Tol *et al*., 2001). Histological re-evaluation after tubal reconstructive surgery due to peritubal or peri-ovarian adhesions has shown residual starch from powdered gloves (Yaffe *et al*., 1980).

A causal connection has been shown between operative tissue damage, intra-abdominal ischaemia, infections, reactions to foreign materials such as sutures, particles of gauze, glove dusting powder and post-operative adhesions

(Myllärniemi, 1967; Holmdahl *et al*., 1996). One of the proven causes of post-operative intestinal adhesions is microscopic foreign bodies which are present in up to 93% of adhesions (Duron *et al*., 1997). After open abdominal or pelvic surgery, a third of the patients are readmitted at least twice during the subsequent 10 years for a disorder directly or possibly related to adhesions (Ellis *et al*., 1999).

Our previous investigation in a rabbit model indicated a retrograde migration of glove powder from the vagina into the intra-abdominal cavity (Edelstam *et al*., 1997). The amount that reaches the peritoneum is sufficient to significantly increase formation of post-operative adhesions after a standardized trauma (Sjösten et el., 2000).

Therefore, this subsequent study in humans was done to investigate whether starch particles from powdered gloves also in humans might gain access to the abdominal cavity through the vagina after a gynaecological examination with powdered gloves.

Materials and methods

Patients

The participants in the study were divided into four different groups. Informed consent was obtained from all participants. All had a routine gynaecological examination before an elective laparotomy for total or subtotal hysterectomy due to fibroids or menometrorrhagia. Group I: examined 1 day pre operatively with (i) powdered gloves (Gammex® Ansell GmbH, Germany; n = 17, mean age 51 years) or (ii) powder free gloves (Biogel® Regent Medical, SLL) (n = 15, mean age 51 years). Group II: examined 4 days pre operatively with (i) powdered gloves (n = 12, mean age 53 years) or (ii) powder free gloves (n = 14, mean age 52 years). Patients with cancer of the uterus were excluded as well as women with ongoing menstrual bleeding. The pre menopausal women were examined regardless of the follicular or luteal phase of the menstrual cycle. A third of all women in the study were post menopausal. Any medication that might have influenced the tubal patency had not been taken except in the case of three patients who had an asthmatic disease and needed to take terbutaline occasionally. The medication was not taken during the investigations. There were no other significant differences for patient characteristics. Sexual activity, cyclic changes or hormonal effect where not considered in this study.

Surgical procedure

An abdominal subtotal or total hysterectomy was undertaken with the operating team and the nurse who set up the instrument tray wearing powder free gloves. Immediately the abdominal cavity was opened, peritoneal fluid was collected and cell smears were then taken from the peritoneal fluid. From the fimbriae of the Fallopian tubes, additional cell smears were taken per operatively and when the uterus had been removed, i.e. post operatively from the uterine cavity and the cervical canal. For making the smears sterile, forceps or peans were used. Smears from the fimbriae of the Fallopian tubes were omitted if they were not removed during the hysterectomy.

Cell smears

The cell smears were quantitatively standardized on ~1 cm^2 of one half of a glass slide with the other blank side serving as control for contamination with air borne starch particles. All the slides were stained with May Grünewald Giemsa by a biochemical assistant wearing powder free gloves in a laboratory where only powder free gloves were used. The slides were coded and analysed by two independent investigators with a Zeiss 4/76 microscope using polarized light at magnification ×250. The starch particles were counted in a standardized procedure for all slides. The numbers on the blank side (i.e. contamination) were subtracted from that in the smears so that the number of starch particles on each slide represent the net number without contaminating particles. Since there are differences in the size of starch particles they where divided into two sizes: (i) smaller than a leukocyte and (ii) larger than a leukocyte. Leukocytes for comparison in size were always present in the smears. The study was approved by the local ethics committee.

Table I. Small and large starch particles on day 1 after examination with powdered (Ia) and powder free (Ib) gloves respectively

		No. of patients	Total no. of particles	Median	Range	Mean	P
Cervix							
Small	Ia	17	70	1	14	4.1	< 0.001
	Ib	15	0	0	0	0	
Large	Ia	17	46	0	24	2.7	< 0.01
	Ib	15	1	0	1	0.01	
Uterus							
Small	Ia	17	104	2	48	6.1	< 0.01
	Ib	15	0	0	0	0	
Large	Ia	17	22	0	10	1.3	< 0.01
	Ib	15	1	0	1	0	
Fallopian tubes							
Small	Ia	12	34	1.5	16	2.8	< 0.01
	Ib	13	0	0	0	0	
Large	Ia	12	18	0	10	1.5	< 0.05
	Ib	13	0	0	0	0	
Peritoneal fluid							
Small	Ia	13	13	1	4	1.0	NS
	Ib	13	3	0	3	0.2	
Large	Ia	13	12	0	6	0.9	< 0.05
	Ib	13	0	0	0	0	

NS not significant.

Statistics

Non parametric Mann Whitney U tests and Fisher's exact test were used and values are given as SEM for the group. Differences were considered significant at the $P < 0.001$, $P < 0.01$ and $P < 0.05$ levels. All statistical tests were computerized and carried out with statistics programs (Statistica™; Statsoft, USA).

Results

Group I: examined 1 day pre-operatively with (i) powdered gloves (n = 17) and (ii) powder-free gloves (n = 15)

Starch particles were found in the cell smears with more particles found on the slides from the patients examined with powdered gloves. The differences were significant at all locations in the genital tract for small particles (cervix $P <$ 0.001, uterus and Fallopian tubes $P < 0.01$) and large particles (cervix and uterus $P < 0.01$ and Fallopian tubes $P < 0.05$) but only for large particles in the peritoneal fluid ($P < 0.05$). However, in two patients examined with powdered gloves, no particles were found. On the contrary, in three patients examined with powder-free gloves, a few particles were found (Table I and Figure 1).

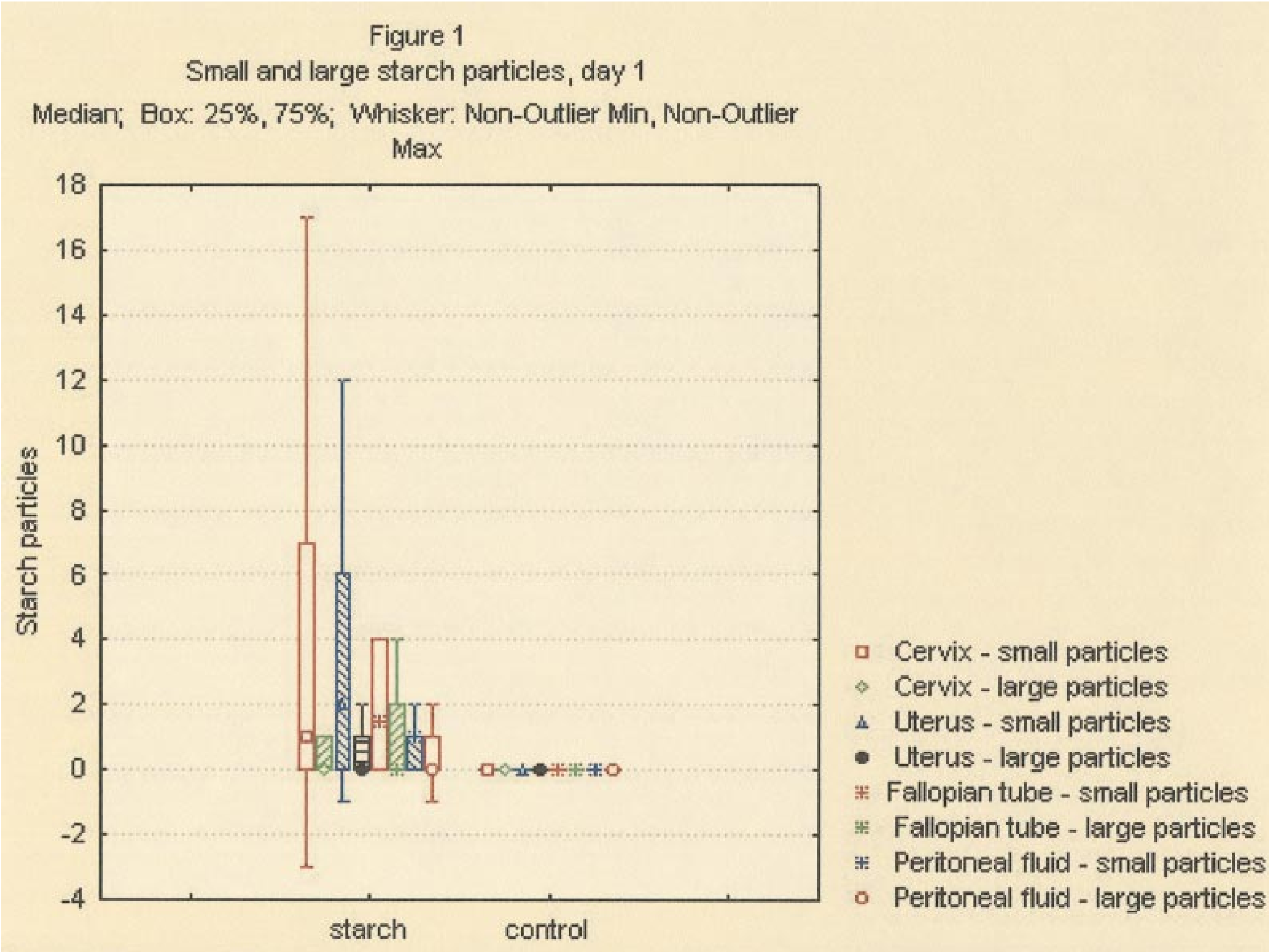

Figure 1. Median and range value for the retrograde transportation of small and large starch particles respectively, in different locations 1 day after a gynaecological examination with or without powdered gloves. The negative range value in the starch group for cervix, uterus and peritoneal fluid are due to contamination with airborne starch particles.

Group II: examined 4 days pre-operatively with (i) powdered gloves (n = 12) and (ii) powder-free gloves (n = 14)

There were significantly more small starch particles as well as large particles (cervix and uterus $P < 0.05$) after examination with powdered gloves. The differences were the same for small particles but less significant for large particles (uterus $P < 0.05$). The differences were non-significant in the Fallopian tubes and the peritoneal fluid (Table II and Figure 2.

Table II. Numbers of small and large starch particles after examination with powdered (IIa) and powder free (IIb) gloves respectively, day 4

		No. of patients	Total no. of particles	Median	Range	Mean	*P*
Cervix							
Small	IIa	12	26	1	2	2.1	< 0.05
	IIb	14	0	0	0	0	
Large	IIa	12	9	0	3	0.8	< 0.05
	IIb	14	0	0	0	0	
Uterus							
Small	IIa	12	21	3	20	1.8	< 0.01
	IIb	14	2	0	0	0.1	
Large	IIa	12	7	0	3	0.6	< 0.05
	IIb	14	0	0	0	0	
Fallopian tubes							
Small	IIa	11	16	1	5	1.4	NS
	IIb	14	4	0	1	0.2	
Large	IIa	11	2	0	1	0.2	NS
	IIb	14	0	0	0	0	
Peritoneal fluid							
Small	IIa	9	14	1	5	1.6	NS
	IIb	11	3	0	1	0.3	
Large	IIa	9	2	0	1	0.2	NS
	IIb	11	0	0	0	0	

NS not significant.

Discussion

Medical gloves for use in surgery were introduced in 1896. Since then, several additives have been tried to facilitate manufacturing and to reduce the hazards associated with glove use (Ellis, 1990). Rubber and glove lubricants are the two main components in modern gloves. Starch powder as a glove lubricant can lead to complications such as granulomatous peritonitis (Giercksky *et al.*, 1994), adhesion formation (van den Tol *et al.*, 2001) and potentiation of infection (Renz and Gemsa, 1997), with subsequent intestinal obstruction, infertility and chronic pelvic pain.

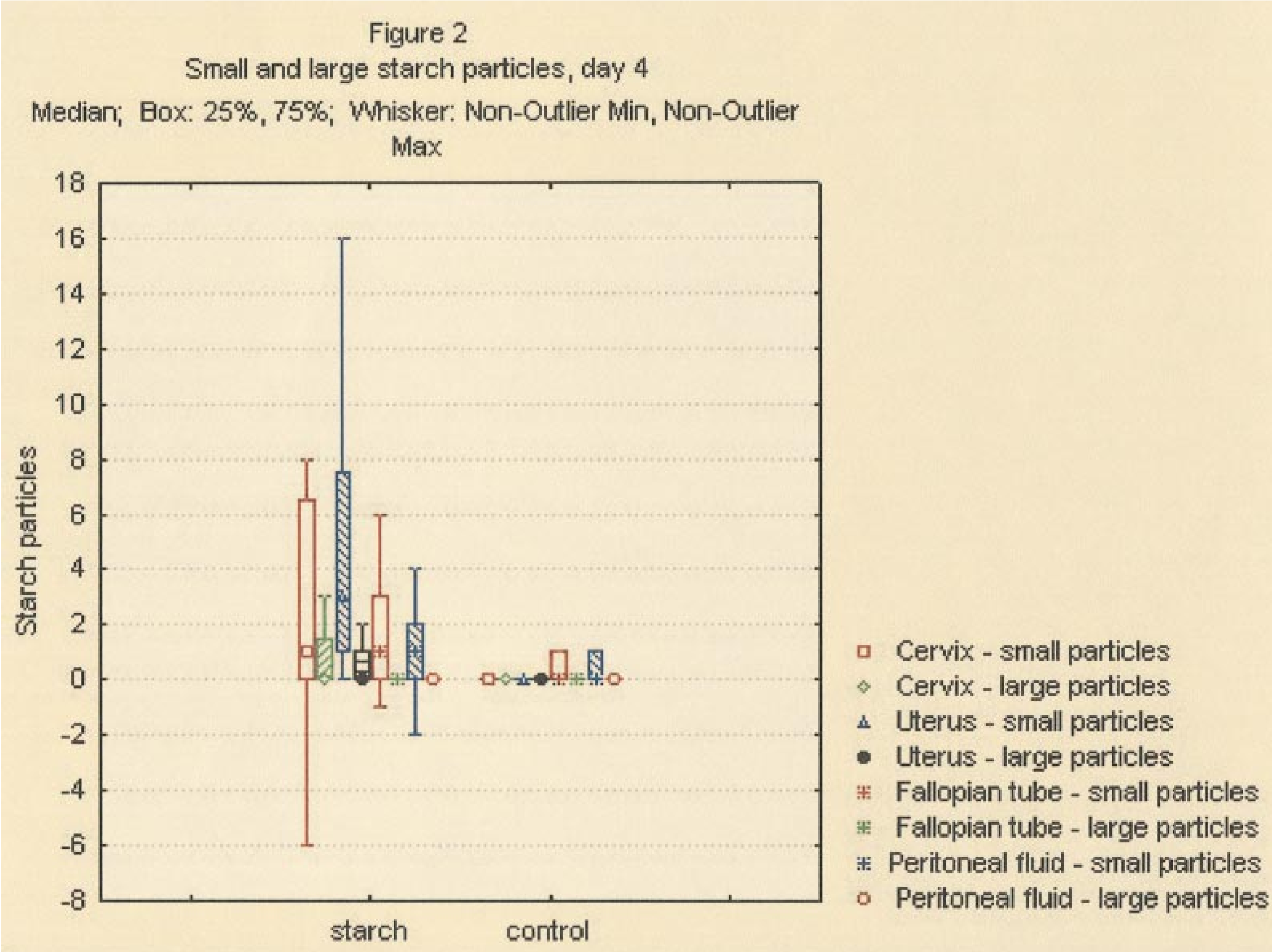

Figure 2. Median and range value for the retrograde transportation of small and large starch particles respectively, in different locations 4 days after a gynaecological examination with or without powdered gloves. The negative range value in the starch group for cervix, Fallopian tube and peritoneal fluid are due to contamination with airborne starch particles.

The possibility of retrograde migration of starch particles in the female genital tract into the intraperitoneal cavity has been suspected for several decades (Saxen *et al*., 1963). The present study in humans has attempted to investigate whether previous results from animal research that starch particles can migrate from the vagina into the abdominal cavity (Edelstam *et al*., 1997) reflects the case in humans. This study indicates such a retrograde migration of starch particles after gynaecological examination with powdered gloves. There were statistically significant differences between study and control groups in cervix, uterus and Fallopian tubes on the first day after vaginal examination with powdered gloves compared to powder-free examination. The low number of starch particles in the cell smear of the peritoneal fluid may reflect differences in the total amount of fluid and that it might have been better to collect all the fluid and after centrifugation prepare cell smears. However, with the present approach a significant difference between pre-operative examination with powdered and powder-free was demonstrated. The lower number of particles on the fourth day might indicate that absorption of starch particles had started, or that the particles had adhered to the peritoneum. In previous animal studies, most particles were found on the third day after deposition in the vagina (Edelstam *et al*., 1997). The numbers found in the controls indicate that the presence of starch particles in the peritoneal cavity is in accordance with reported persistance for up to 18 months (Ellis, 1971). Our present patients have been examined in that time before the referral for hysterectomy.

A considerable number of gynaecologists wears starch-powdered gloves (Sjösten *et al*., 1999), despite evidence of starch-induced complications. The starch particles can migrate not only from the vagina into the cervical canal and the uterine cavity but also through the Fallopian tubes into the peritoneal fluid. Women exposed to intra-abdominal surgical trauma 1 4 days after a gynaecological examination with powdered gloves may be at increased risk of intra-abdominal adhesions. But even without a surgical procedure there is a risk of intra-abdominal or peri-tubal adhesions due to the examination with powdered gloves (Osser *et al*., 1989). Ongoing subclinical PID can cause infective tissue damage. An extensive study by Myllärniemi (1967) showed that talc, starch powder and lint in the abdominal cavity tended to accumulate in the traumatized areas of the peritoneum so that the foreign material contaminating the peritoneal tissues could act together with other

traumatizing conditions, possibly preventing the resorption of fibrinous adhesions. This corresponds to our previous finding in the rabbit model that starch particles deposited in the vagina can migrate in a retrograde direction from the vagina into the abdominal cavity and, combined with an intra-abdominal trauma, generate dense adhesions (Sjösten *et al*., 2000). Since there are indications towards retrograde migration of powder, it must not be used regardless of cyclic variations or sexual activity.

In conclusion, our results show that starch particles can migrate from the vagina into the cervical canal, the uterine cavity and through the Fallopian tubes up to 4 days after a gynaecological examination with powdered gloves. Glove powder contributes to adverse intra-abdominal reactions, which include adhesion formation and adhesion-related complications such as chronic pelvic pain and bowel obstruction. Tubal and pelvic adhesions are a major cause of female infertility. Since evidence suggests that a retrograde migration could be a general mechanism, our recommendation is that we should be critical of harmful substances, e.g. glove powder, that could migrate from the vagina to abdominal cavity.

Acknowledgements

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Exhibit 21

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

RULE 26 EXPERT REPORT OF PATRICIA G. MOORMAN, MSPH, PHD

Date: November 16, 2018

Patricia G. Moorman

Patricia G. Moorman, MSPH, PhD

Scientific Review of the Epidemiologic Evidence on Talc Use and Ovarian Cancer

Patricia G. Moorman, MSPH, PhD

Professor, Department of Community and Family Medicine

Cancer Control and Population Sciences, Duke Cancer Institute

Duke University School of Medicine

Durham, NC

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Background and Qualifications of Patricia G. Moorman, MSPH, PhD

I am a tenured professor in the Department of Community and Family Medicine, Duke University School of Medicine, Durham, NC and a member of the Cancer Control and Population Sciences Program in the Duke Cancer Institute. I am an epidemiologist with more than 25 years of experience in conducting research on women's health issues including ovarian cancer, breast cancer and menopause. Attached as Exhibit A to this report is a current copy of my curriculum vitae.

Education

I received a Bachelor of Science degree with distinction in pharmacy from the University of Kansas in 1980. I pursued graduate studies in epidemiology in the School of Public Health at the University of North Carolina-Chapel Hill, earning a Master of Science in Public Health (MSPH) in 1989 and a Doctor of Philosophy (PhD) degree in 1993.

Professional Experience

I have held positions in academic institutions since I completed my PhD, beginning as a research assistant professor in the Department of Epidemiology at the University of North Carolina-Chapel Hill from 1994 through 1996. From 1997 to 2000, I was an associate research scientist in the Chronic Disease Epidemiology division of the Yale University School of Public Health. I came to Duke University School of Medicine as an assistant professor in 2000, progressing through the academic ranks from associate professor, associate professor with tenure to my current position as professor in Community and Family Medicine. I also serve as the director of the Clinical Research Unit for the Department of Community Medicine and am a member of the Senior Faculty Advisory Committee for the Office for Research Mentoring in the School of Medicine. In addition, I am an adjunct faculty member in the Department of Epidemiology at the University of North Carolina-Chapel Hill.

Compensation and Testimony

My hourly billing is $400. I have given deposition testimony in one case (Gail Ingham, et al., v. Johnson & Johnson, et al., Case No. 1522-CC10417-01, Circuit Court of the City of St. Louis, Division 10) and have not testified at trial in the last four years.

Research Interests and Experience

My primary research interests are in the area of women's health issues, with a particular focus on studying racial differences in risk factors and outcomes. I have had funding from the National Institutes of Health (NIH) for more than 20 years, which has supported my research in ovarian cancer, breast cancer and ovarian function after hysterectomy. Three of the key studies in my research career are: 1) the African American Cancer Epidemiology Study (AACES), a multi-center, case-control study of ovarian cancer in African American women,[1] 2) the Carolina Breast Cancer Study, which is one of the largest studies focused on understanding racial differences in breast cancer risk and outcomes,[2] and 3) the Prospective Research on Ovarian Function (PROOF) Study, a cohort study designed to examine risk for ovarian failure after premenopausal hysterectomy.[3]

Each of these studies involved primary data collection, meaning that the investigative team designed the data collection procedures, developed the surveys, recruited study participants and obtained questionnaire data and biological specimens from the participating women. Each study has made unique contributions to the scientific literature.

AACES has enrolled more than four times as many African-American women with ovarian cancer than any other study and is providing the most comprehensive epidemiologic data on ovarian cancer risk factors in this population to date.[4-6] The Carolina Breast Cancer Study likewise provided key data on risk factors in African American women and was the first study to describe the markedly higher prevalence of the poor-prognosis basal subtype of breast cancer in young African American women.[7-11] The PROOF study is the largest prospective study of ovarian function after pre-menopausal hysterectomy and demonstrated that women

undergoing hysterectomy with ovarian conservation were at significantly increased risk for earlier menopause as compared to women who did not have a hysterectomy.[3,12]

Our study team published an analysis of talc exposure and ovarian cancer in 2016, using data from AACES. [13] This peer-reviewed paper, published in *Cancer Epidemiology, Biomarkers and Prevention*, was the first epidemiologic study of talc use and ovarian cancer that was focused exclusively on African American women. Our analyses found both a high prevalence of talc use in this study population and a statistically significantly increased risk for ovarian cancer among talc users. This paper was published prior to my involvement in litigation related to talc and ovarian cancer.

I have also been a co-investigator on the North Carolina Ovarian Cancer Study, which was a precursor to the AACES study. Data from this study were included in Terry, et al.'s [14] 2013 analysis of genital powder use and ovarian cancer that pooled from data from eight case-control studies. I am currently an investigator in the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium. The OCWAA consortium, which was initiated in 2016, is a multi-center collaboration that aims to bring together data from case-control and cohort studies to evaluate similarities and differences between African American and white women in ovarian cancer risk factors and outcomes.

In addition to these studies, I am an investigator with the Evidence Synthesis Group in the Duke Clinical Research Institute, a team of researchers that conducts evidence reviews of the scientific literature. I have worked with this group on a number of systematic reviews and meta-analyses on women's health issues including an evaluation of the benefits and risks of oral contraceptive use for primary prevention of ovarian cancer [15-17] funded by the Agency for Healthcare Research Quality, and an evaluation of the benefits and harms of breast cancer screening[18] funded by the American Cancer Society to help inform their screening mammography recommendations.[19]

I am an author on more than 130 scientific publications, with more than 50 of them directly related to ovarian cancer. The ovarian cancer papers address a wide variety of risk factors including reproductive and hormonal factors, lifestyle characteristics, genetic factors, and talcum powder products. The main focus of the manuscripts on which I have been the lead

author has been ovarian cancer risk factors in African American women and the effects of reproductive characteristics, hormones and other medications on risk for ovarian cancer.[5,17,20-23] The papers have been published in some of the leading journals in the field of epidemiology, gynecology and cancer including the *American Journal of Epidemiology, Cancer Epidemiology Biomarkers and Prevention, Obstetrics & Gynecology* and *Journal of Clinical Oncology*.

My teaching experience includes courses in Cancer Epidemiology for graduate students in public health and Evidence-Based Medicine for physician assistant students. A primary emphasis of these courses has been for the students to gain an understanding of the advantages and disadvantages of different types of studies used in clinical and epidemiologic research. In particular, the Evidence-Based Medicine course is designed to help the students learn how to critically appraise the medical literature and apply findings to clinical practice. In addition, I have mentored at the individual level public health graduate students and medical students.

I serve as an editorial reviewer for numerous journals and have served as a peer reviewer of grant applications on several dozen study sections over that past twenty years. I have reviewed NIH grants for a variety of funding mechanisms ranging from small grants (R03) to large multi-project applications (SPORE grants and Program Projects). I also have served as both peer reviewer and study section chair for the Susan G. Komen for the Cure Foundation and the Department of Defense Ovarian Cancer and Breast Cancer Research Programs.

In summary, in a career spanning more than 25 years, I have devoted my efforts to understanding factors that affect risk for ovarian cancer, breast cancer and menopause. I have conducted original research, giving me a deep appreciation of the advantages and disadvantages of different study designs and the challenges of collecting high-quality data for making etiologic inferences. I also have conducted research involving synthesis of the published literature, with the goal of informing decisions based on the best available evidence. A large proportion of my publications have focused on the epidemiology of ovarian cancer, and many of the others focused on breast cancer or menopause have relevance to ovarian cancer because of shared risk factors for the conditions. Based on my education, experience, and expertise, I

am highly qualified to assess the literature on the use of talc in relation to ovarian cancer and provide an expert opinion to a reasonable degree of medical certainty.

Purpose

The purpose of this report is to summarize the epidemiologic evidence related to talc use and ovarian cancer risk and to make a judgment as to whether there is sufficient evidence, based on the totality of evidence from epidemiologic investigations as well as laboratory and mechanistic studies, to conclude with a reasonable degree of scientific certainty that talcum powder use Is a causal factor for ovarian cancer.

Throughout the report, the term "talc" will be used to refer to talcum powder products, recognizing that commercial talc products can contain asbestos, talc containing asbestiform fibers (e.g., talc occurring in a fibrous habit), heavy metals such as nickel, chromium and cobalt and fragrances.

Role and Importance of Epidemiologic Studies

It is important to bear in mind that epidemiologic research on factors that are thought to increase risk for cancer in human populations will consist of observational rather than experimental studies. As with most other now-known carcinogens, including cigarette smoke, it is both ethically wrong and pragmatically impossible to conduct randomized controlled trials to investigate whether a given exposure increases risk for cancer in humans. The judgment as to whether talc causes ovarian cancer will be based on epidemiologic studies in which the investigators collected and analyzed information on exposures (i.e., talc use and other risk factors) that the study participants chose to use, rather than studies in which exposures were randomly assigned to the study subjects in an experimental setting.

Observational study designs used in the study of talc and ovarian cancer include cohort and case-control studies, both of which are well-established and generally accepted methods for studying cancer etiology. In a prospective cohort study, a large group of individuals (the cohort) is identified and exposure to various factors hypothesized to affect risk of disease is

assessed at the time of enrollment (baseline). The cohort is followed over time and the analyses focus on whether the exposed group is more or less likely to develop the outcome of interest than the unexposed group. Some of the prominent advantages of cohort studies are that multiple outcomes/diseases can be assessed within the cohort and exposure assessment precedes the development of the disease, limiting recall bias. However, a primary disadvantage of cohort studies, particularly in relation to cancer etiology studies, is that they must enroll tens of thousands of subjects and follow them for long periods of time to accrue enough cases to have a well-powered study. In addition, if cohort studies do not update exposure information after the baseline assessment, the exposure of some individuals in the cohort may be misclassified.

Case-control studies identify individuals with the disease of interest and an appropriate control group of individuals without the disease and assess exposures that are thought to increase or decrease the risk of the disease. The investigators then analyze whether cases are more likely than the controls to have a given exposure. Case-control studies focus on a single disease, therefore they typically collect more detailed risk factor information for that disease than cohort studies. A major advantage of case-control studies is that they are a more efficient design for studying diseases that are less common or have a long latency period. Therefore, they are very commonly used for etiologic studies of cancer. A disadvantage of case-control studies is that they collect exposure information for the cases after they have already been diagnosed with the disease, which raises concerns that cases may recall exposures differently from controls.

Cohort studies and case-control studies each have advantages and disadvantages for assessing talc as a risk factor for ovarian cancer, and one study design is not clearly superior to the other. In addition, specific details related to the conduct of the study such as methods of exposure assessment, length of follow-up and choice of control group can impact the validity of the findings and the interpretation of results. Therefore, rather than making a judgment based only on the overall study design, the evaluation and interpretation of the findings of the studies must consider the strengths and weaknesses of the individual studies. As the results of the

studies are described and evaluated in this report, specific advantages and disadvantages of individual studies will be discussed in more detail.

In contrast to studies on laboratory animals, studies on humans are subject to more variation in exposure assessment and it is impossible to control all other factors that may contribute to disease risk. For these reasons, judgments on causality from epidemiologic research typically are not based on a single study or even a few studies, but are based on the totality of evidence from multiple studies conducted in different study populations, in different locations and across different time periods. Evidence from the epidemiologic investigations is combined with relevant studies from other disciplines, including pathology, animal and mechanistic studies, to make an assessment of the evidence for a causal association between genital exposure to talcum powder and ovarian cancer.

Methodology

The methodology I used to assess the epidemiologic evidence on talc use as a causal risk factor for ovarian cancer involved conducting a literature search on PubMed using the terms “ovarian cancer” and “talc” to identify all relevant original studies, systematic reviews, meta-analyses, editorials and commentaries (search most recently updated on October 29, 2018). The search I did returned 131 articles, all of which were systematically considered and assessed as to their relevance to talc as a risk factor for ovarian cancer. Twenty-nine articles were not directly relevant to the question at hand (mostly addressing talc in the treatment of malignant pleural effusions). Of the remaining 101 articles, 36 were reports of original epidemiologic studies directly addressing genital talc exposure and ovarian cancer or meta-analyses of such studies.[14,24-56] Other articles retrieved included studies of occupational talc exposure,[57-62] other original research articles that were not specifically epidemiologic studies of genital talc and ovarian cancer (e.g., studies of endometrial cancer, pathology studies, animal studies, etc.)[63-80] and reviews, commentaries and letters [60,81-120] I also examined reference lists from key articles to identify any additional relevant studies. In addition, I reviewed relevant studies as well as documents provided during the course of discovery process.

The primary focus of my review is the epidemiologic studies of genital talc exposure and ovarian cancer and the meta-analyses, with supporting information from other types of publications, including animal, pathology and mechanistic studies used as appropriate to address biological mechanisms underlying the association between talc use and ovarian cancer.

As I evaluated the individual epidemiologic studies (case-control and cohort studies) that described the risk for ovarian cancer associated with talc use, I did not weight one design more heavily than the other because there are advantages and disadvantages to each design for evaluating talc as a cause of ovarian cancer. I considered the potential biases of individual studies, both those that supported and those that did not support an association between talc and ovarian cancer, and how those biases may have impacted the findings. As I describe in this report, some biases have the potential to lead to an overestimate of the relative risk (e.g. recall bias in case-control studies) while others could result in an underestimate of the relative risk (e.g. incomplete ascertainment of talc use in the cohort studies).

I also considered the studies that combined data from multiple studies – meta-analyses or pooled analyses from multiple case-control studies. These types of analyses are often considered to be some of the strongest evidence for a causal association between an exposure and disease as they provide an estimate of the relative risk that is more statistically robust than individual studies. Data from meta-analyses are particularly important for evaluating exposure-disease relationships such as talc and ovarian cancer where the relative risks from most individual studies are approximately 1.2 to 1.5.

As is standard in epidemiologic research, my assessment of whether there is a causal association between talc use and ovarian cancer was guided by the aspects of a causal relationship described by Bradford Hill during the 1960's. Sir Austin Bradford Hill's writings on causal inference provide an accepted framework for assessing whether a given exposure is a cause of a specific outcome.[121] The aspects of the associations that Hill described are: Strength, Consistency, Specificity, Temporality, Biological Gradient, Plausibility, Coherence, Experiment and Analogy. As his writings clearly state, these viewpoints or perspectives should be taken into account when assessing causality, but are not to be considered absolute criteria and not all must be checked off to make a conclusion of a causal relationship. Specifically, he states "What

I do not believe is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*." This list of viewpoints was used to guide my assessment of the scientific literature on talc use and ovarian cancer.

It is important to point out that, in the end of this process, the assessment of whether a substance is or is not a causal risk factor for a given disease or condition involves scientific judgment that is made by considering and weighing the evidence. In any given case, it is not unusual for scientists and epidemiologists to weigh the Hill factors differently in reaching a conclusion on the causal inference in question. For example, scientists for many years debated the evidence that cigarette smoking causes lung cancer or asbestos causes lung disease.

Epidemiologic Studies Reviewed

Since 1982, when the first case-control study describing an increased risk for ovarian cancer associated with talc use was reported by Cramer, et al., [50] more than two dozen additional reports of epidemiologic studies have been published.[13,14,24-36,38-44,46-49,51-55,122,123] In some instances, data from a particular study were included in more than one publication, due either to an additional analysis of data from a cohort study with longer duration of follow-up (e.g., [31,34]) or to analyses that combined data from more than one study (e.g., [14,25]). Included in these publications are seven meta-analyses published between 1992and 2018 that combined overall results from nine to 27 studies [35,51,52,54-56]and a pooled analysis published in 2013 that combined individual level data from eight case-control studies.[14]

Strength and Consistency of the Association

The first two aspects of the causal relationship described by Bradford Hill, strength and consistency of association, are deeply intertwined. While Bradford Hill referenced the assumption that a larger relative risk is more likely to reflect a causal association, Hill also clearly stated that we should not be "too quick to dismiss a cause-and-effect hypothesis merely

on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so." [121]

Seven meta-analyses of genital talc exposure and ovarian cancer [35,44,51,52,54-56] calculated summary relative risks that were very consistent across the publications, ranging from 1.22 to 1.36, all with 95% confidence intervals excluding 1, indicating that women who reported talc use were at statistically significant increased risk for ovarian cancer. Similarly, the pooled analysis of eight case-control studies reported an overall odds ratio of 1.24 (95% confidence interval (CI) 1.15 – 1.33).[14]

To put this in context, it is useful to compare the epidemiologic data related to the strength of the association between genital talc use and ovarian cancer with some other well-accepted exposure-disease associations that have relative risks of similar magnitude and are generally accepted to be causal associations. Some examples of such associations and the relative risks from these exposures estimated from meta-analyses are:

1. Oral contraceptive use and breast cancer, relative risk 1.08 (95% CI 1.003-1.165) for ever versus never use and relative risk 1.21 (95% CI 1.04-1.41) for current or recent use versus never use[16]
2. Menopausal estrogen use and breast cancer, relative risk 1.20 (95% CI 1.06-1.37) for more than 5 years use versus no use[124]
3. Passive smoking (also referred to as environmental tobacco exposure or secondhand smoke) and lung cancer, relative risk 1.27 (95% CI 1.17-1.37) for ever versus never exposure to a spouse who smoked[125]
4. Residential radon exposure and lung cancer, relative risk 1.29 (95% CI 1.10-1.51) for highest versus lowest exposure[126]
5. Trichloroethylene exposure and kidney cancer, relative risk 1.32 (95% CI 1.17-1.50) for occupational exposure.[127]

Each of these exposure/disease associations is widely accepted as a causal relationship in the scientific community and has been judged to be a causal association by the International Agency for Research on Cancer (IARC). [128-130] [131] The estimates of the relative risks for these associations from meta-analyses or pooled analyses are approximately 1.25,[16,124-126,132,133]

which is in the range of estimates of the relative risk from meta-analyses and pooled analyses for the association between genital talc use and ovarian cancer. Therefore, we have evidence of well-established causal associations in which the magnitude of the relative risk is very similar to what has been reported for genital talc use and ovarian cancer.

It is instructive to compare in more detail the epidemiologic data on passive smoke exposure to that of talc and ovarian cancer. Passive smoke exposure, like talc, is a very common exposure in the population that can only be assessed retrospectively through self-report, therefore it is difficult to determine the precise level of exposure. In a meta-analysis of 55 studies published between 1981 and 2006 that examined the risk for lung cancer in never smoking women with passive smoke exposure from their spouses, Taylor, et al. [125] reported a pooled relative risk of 1.27 (95% CI 1.17-1.37). The relative risks from individual studies ranged from 0.66 to 2.57, with 44 of the 55 (80%) individual studies reporting a relative risk or odds ratio >1. In the individual studies, only 10 of 55 (18%) reported statistically significant associations (2 of 7 cohort studies, 3 of 25 case-control studies with population-based controls and 5 of 23 case-control studies). These data show that among the many epidemiologic studies that assessed passive smoke exposure as a risk factor for lung cancer, not all had statistically significant findings and some even reported relative risks less than one, yet the overall conclusion from the totality of the evidence is that passive smoke exposure is causally associated with lung cancer.

The most recent meta-analysis published in 2018 on talc and ovarian cancer by Pennikilampi et al. reported a pooled relative risk of 1.31 (95% CI 1.24-1.39) with values from individual studies ranging from 0.73 to 3.90.[56] This result is consistent with other meta-analyses performed. Twenty-four of the 26 (92%) studies reported a relative risk or odds ratio >1, and statistically significant associations were reported in 14 of the 26 (54%) studies. This comparison illustrates that as compared to the well-established causal association between passive smoke exposure and lung cancer, the association between talc and ovarian cancer has a pooled relative risk estimate of similar magnitude with a greater proportion of the studies reporting relative risks >1 and a greater proportion reporting statistically significant

associations suggesting the evidence for talc and ovarian cancer is as significant as for passive smoke exposure and lung cancer.

These comparisons also illustrate the importance of meta-analyses in epidemiologic research when considering exposures for which the strength of association is approximately 1.5 or less. Individual studies, especially those with smaller samples sizes, may not detect a statistically significant increased risk. When the increased risks in this range are seen repeatedly, even when individual studies are not statistically significant, meta-analysis allows the data to be aggregated to make a conclusion that is more robust statistically. When combining these studies through meta-analysis, the totality of the data shows that there is indeed a statistically significant link between genital talc use and ovarian cancer. This observation has been quite consistent, with findings replicated in studies conducted by different teams of investigators, in different geographic locations within and outside the United States, in different race/ethnic groups and over a span of several decades.

In conjunction with the strength of the association, it is also critical to consider the prevalence of the exposure in the population when evaluating its public health impact. A risk factor that is less strongly associated with a disease but has a high prevalence in the population can be responsible for more cases of the disease than a risk factor that is more strongly associated with the disease but has a low prevalence in the population. A measure of the contribution of a risk factor to a disease is the population attributable fraction (PAF), which is defined as the proportion by which the incidence rates of the outcome in the population would be reduced if the exposure was eliminated.[134] Wu et al. [26] calculated the PAF for ovarian cancer related to talc exposure in their multi-ethnic case-control study in Los Angeles. The odds ratio for genital talc use was 1.46 (95% CI 1.27 – 1.69) and the prevalence of use was 41% among the cases and 31% among the controls. The PAFs for the different ethnic groups ranged from 12.2 to 15.1%, which is interpreted as the proportion of ovarian cancer cases that theoretically could be prevented if genital talc use in the population could be eliminated and there were no changes in other risk factors. In other words, of the estimated 22,440 cases of ovarian cancer diagnosed in 2017,[135] approximately 3,300 of them could theoretically have been prevented if women had not used genital talc. The PAF calculation demonstrates that even with an

estimated relative risk for genital talc use of less than 1.5, its high prevalence of use means that it contributes to a substantial proportion of the ovarian cancer cases in the population.

The overall associations seen in the talc-ovarian cancer meta-analyses as well as in many of the individual studies are statistically significant, indicating an increase in risk of approximately 25 to 30%. While not as high as other relationships like smoking and lung cancer, these relative risks are in line with other generally accepted causal relationships (e.g., second hand smoke and lung cancer). I consider the strength of the association seen in the talc-ovarian cancer epidemiologic studies, to be an important factor in favor of a causal relationship between talc and ovarian cancer, particularly when considered along with the consistency of the association sees across these studies.

As described above, among the more than two dozen studies that have reported on the association between talc use and ovarian cancer, the vast majority of them reported relative risks or odds ratios greater than one, indicating strong consistency in the direction of the effect. The findings from the multiple studies are summarized in seven meta-analyses published since 1992, including two published in 2017-18, that combined overall results from six to 27 studies assessing genital talc exposure and ovarian cancer [35,51,52,54,55] [56] [44] and in a pooled analysis published in 2013 that combined individual level data from eight case-control studies. [14] Of the 27 studies included in Berge et al.'s 2017 meta-analysis [51], 24 were case-control studies (18 population-based,[13,23,25,29,30,32,33,38,39,41,42,44,45,47,50,123,136,137] 5 hospital based, [36,43,46,49,122] and 1 with both hospital and population controls [48]) and three were prospective cohort studies [24,27,31]. The calculated overall relative risks for all studies combined in these meta-analyses were 1.3 (95% CI 1.1 – 1.6),[44] 1.27 (95% CI 1.09-1.48),[55] 1.36 (95% CI 1.24-1.49),[35] 1.33 (95% CI 1.16-1.45),[54] 1.35 (95% CI 1.26 - 1.46),[52] 1.22 (95% CI 1.13-1.30)[51] and 1.31 (95% CI 1.24-1.39)[56] and 1.24 (95% CI 1.15-1.33) in the pooled analysis of eight case-control studies.[14] The conclusions from these analyses were quite consistent, even with additional data accumulating over time, indicating that women who used talc products as compared to women who reported no talc use were at 22 to 36% increased risk for ovarian cancer.

When considering the consistency from a number of different studies and meta-analysis, an epidemiologist should evaluate potential sources of bias including but not limited

to publication bias, recall bias, selection bias and information bias. I discuss each of these below.

Publication Bias: When considering a body of epidemiologic evidence from multiple studies, several concerns arise about the completeness of the published data and whether there is selective publishing of studies that find significant positive associations. These concerns were addressed by two distinct analyses conducted in the most recent meta-analyses by Berge, et al. (2017) and Penninkilampi and Eslick (2018).[51,56] The first approach reported was a funnel plot, which is a graphical technique that plots the relative risks derived from the studies on one axis and the standard error of the relative risk (an indicator of the size of the study) on the other. The concept driving this approach is that studies should cluster around the "true" relative risk in the population. Due to random statistical variation, some studies will have relative risks that are higher than the true relative risk and some will be lower than the true relative risk. As sample sizes increase, there should be more precise estimates of the relative risk, therefore larger studies would be expected to produce estimates closer to the true relative risk whereas smaller studies may produce results that deviate further from the relative risk in the overall population. When the study results are plotted, one would expect them to fall into a funnel shape, with the larger studies at the point of the funnel, clustered around the true relative risk in the population, and smaller studies, with more variation in results, showing greater deviation from the average, forming the wide part of the funnel. Notably, in these meta-analyses, the two studies with the highest relative risk estimates (Chen, et al [45] with a relative risk of 3.90 and Godard, et al. [38] with a relative risk of 2.49) and the two studies with the lowest relative risks (Hartge, et al. [49] and Gonzalez, et al. [24]) all had a modest number of cases (<=170).

A funnel plot provides a method for assessing publication bias, i.e., the bias that results from studies with statistically significant findings being more likely to be published than studies that show no association. If one is concerned that studies that showed no association between the exposure and outcome are less likely to be published, the funnel plot allows the visual assessment of this potential bias. A lack of symmetry in the funnel plot, with a deficit of studies showing no association between the exposure and outcome, would be an indication of

publication bias. The papers by Berge, et al. [51] and Penninkilampi and Eslick [56] which are the only meta-analyses that specifically addressed publication bias, concluded that there was no serious publication bias based on both visual inspection of the funnel plot and a statistical assessment of the data from the funnel plot. Therefore, there is a high level of confidence that there has not been preferential publication of studies that found a positive association between talc and ovarian cancer.

A second approach used by Berge, et al. [51] was a cumulative meta-analysis, in which they showed the estimated summary relative risks over time from the first published report in 1982 through the most recently published studies in 2016. The plot showed that after the first initial reports, the overall summary estimates stabilized with estimates in the range of 1.2 to 1.25 over the last 25 years even as more and more data accrued from additional published studies.

These quantitative analyses indicate that it is unlikely that there is publication bias in the talc and ovarian cancer literature (i.e., the analyses do not suggest that studies that found talc use to be a risk factor for ovarian cancer were more likely to be published than those that found no association). Furthermore, from a qualitative perspective, it is also unlikely that there is a substantial risk for publication bias. Given the considerable public health interest in the risk for ovarian cancer associated with a widely-used cosmetic product, it is probable that any well-designed and conducted study that addressed this question would be published, even if it had null findings. Notably, one of the most recent studies, the Sister Study,[24] was published even though it found no increased risk for ovarian cancer associated with talc use.

While the overall conclusions from the meta-analysis and pooled analyses are quite consistent, with an overall statistically significant estimate of the relative risk in the range of approximately 1.2 to 1.3, it is important to consider possible reasons for heterogeneity of the estimates between individual studies.

Among the individual studies that have examined the association between talc use and ovarian cancer, the majority have been case-control studies, with only three prospective cohort studies addressing this research question. The meta-analysis by Berge, et al.[51] noted that the summary relative risk was driven by the stronger associations observed for case-control studies

(relative risk = 1.26 (95%CI 1.17 – 1.35) than for cohort studies (relative risk = 1.02 (95% CI 0.85 – 1.20), which leads one to try to understand possible reasons for the differences by study design and to consider the relative advantages and disadvantages of the different study designs, specifically in relation to the study of talc and ovarian cancer. While the cohort studies do not show a statistically significant association for ever use of talc and ovarian cancer overall, the recent meta-analysis by Penninkilampi and Eslick[56] reported a statistically significant association with the invasive serous subtype of ovarian cancer, which is both the most common subtype and the one with the worst prognosis.

Case-Control Studies – Strengths and Weaknesses: Case-control studies, which are very commonly used in cancer epidemiology, have particular advantages for studying a relatively uncommon cancer like ovarian cancer, which has an annual incidence (number of new cases) in the United States of approximately 11 cases per 100,000 women.[138] In this study design, women with ovarian cancer (the case group) are identified by the research team, typically through a cancer registry, shortly after receiving their diagnosis. A control group of women who do not have the disease are also identified and recruited for the study. Both the cases and the controls provide information on their past exposure history. In a typical case-control study, the study participants complete an extensive questionnaire focusing on a broad range of exposures that are hypothesized to either increase or decrease the risk for cancer. In regard to ovarian cancer, a typical questionnaire will include questions on demographic characteristics, reproductive characteristics like pregnancy and contraception, medical characteristics, family history of cancer and lifestyle characteristics such as dietary factors, smoking history, physical activity and talc use. Notably, some of the factors queried about are expected to increase risk (e.g., family history of ovarian or breast cancer, estrogen use during menopause, talc), whereas others are associated with reduced risk (e.g., oral contraceptive use, pregnancies).

One major advantage of a case-control study is that it is possible to identify and recruit a large number of cases within a relatively short timeframe. To illustrate this point, I will use the example of AACES, the case-control study that my colleagues and I initiated in 2010 to study ovarian cancer in African American women and which was the source of the data we used for our 2016 paper on talc and ovarian cancer.[1,13] We have enrolled more than 600 women with

ovarian cancer and more than 700 control women over a period of approximately 6 years, making it by far the largest study of ovarian cancer in African American women. When the grant application was originally submitted to the National Cancer Institute, one reviewer expressed the opinion that a cohort study would be preferable to the case-control design we proposed. In our response to the review, we pointed out that a prospective cohort study was not feasible for studying ovarian cancer in this population if we hoped to obtain meaningful information in a reasonable timeframe. The Black Women's Health Study, a large prospective cohort study, enrolled approximately 60,000 women starting in 1995 with the goal of studying a wide variety of health outcomes in this population.(https://www.bu.edu/bwhs/) In regard to ovarian cancer, after 18 years of follow-up, only 115 cases of ovarian cancer had been diagnosed among women in the cohort.[139] Although a cohort of 60,000 women is a very large epidemiologic cohort, it is still inadequate to study a relatively uncommon disease like ovarian cancer in a time-efficient manner. We successfully made the argument to the reviewers that a case-control study was the only feasible way to investigate the etiology of ovarian cancer in a timely manner in the African American population. This example illustrates why it is to be expected that the majority of the epidemiologic studies of ovarian cancer would be case-control studies.

Although case-control studies are commonly used in epidemiologic studies of cancer, there are potential biases associated with this study design, including selection bias and recall bias. In this study design, the investigator must select a control group of individuals without the disease being studied as a comparison group to determine the relative frequency of the exposures in the case group as compared to the control group. The goal of selecting a control group is to identify a group that is representative of the population from which the cases arose. This is often stated in textbooks as if someone in the control group were to develop the disease being studied, s/he would have been selected as a case for the study. There are many possible strategies for identifying and recruiting population-based controls, including the use of town registry books,[25,50], telephone recruitment through random digit dialing [13,25,29], neighborhood recruitment,[30] driver's license records [25] and electoral rolls.[123] In hospital-based case-control studies, controls are typically selected from other hospitalized patients, with different studies

applying different criteria for eligible diagnoses among the controls, including other cancer diagnoses or specific non-cancer diagnoses. [36,43,46,49,122]

Among the studies included in the recent meta-analyses, six were hospital-based case-control studies.[36,43,46,48,49,122] The individuals that comprised the control group varied between these studies including patients with non-gynecologic malignancies,[36] patients treated for conditions other than gynecologic or malignant diseases,[122] patients treated for conditions other than those related to reproductive history or oral contraceptive use,[46] patients treated for conditions other than gynecologic, psychiatric, or malignant diseases or pregnancy,[49] both hospital patients and population-based controls [48] and hospital visitors.[43] While the use of hospital controls may be efficient, concerns are often raised as to whether the controls are representative of the population from which the cases arose in terms of the exposures they experienced or their underlying risk for cancer. This is a particular concern with the study by Wong, et al, [36] which is the largest of the hospital-based case-control studies and one that found no association between talc use and ovarian cancer (OR=0.92, 95% CI 0.24-3.62). The control group in this study was "female patients treated for non-gynecologic malignancies during the same period". Standard epidemiologic textbooks (e.g., Rothman, *Modern Epidemiology*[140]) state that controls should be selected from the same source population or study base that gives rise to the cases. It is difficult to make the argument that other cancer patients represent the source population from which the ovarian cancer cases arose, which suggests that this was a poor choice of a control group that could have led to biased findings.

Another of the hospital-based studies, the study by Tzonou et al.[43] which reported a relative risk of 1.05, also had a significant limitation. This study was conducted in Greece, and the overall prevalence of talc use in the study population was 3.5%. Given the small sample size and the low prevalence of exposure, this population was ill-suited to study the relation between talc use and ovarian cancer.

As noted in the meta-analysis by Penninkilampi and Eslick, [56] the hospital-based studies were older (published before 2000) and with the exception of the Wong study [36], all were smaller studies that included fewer than 200 cases. The summary odds ratios from the hospital-based studies was lower but not significantly different than the summary odds ratio from

population-based studies (OR 1.22 versus 1.33, respectively),[56] a result that is not surprising given the important limitations in some of the hospital-based studies.

While there is no ideal method for control selection, arguably population-based control recruitment is more likely to result in a control group that is representative of the population from which cases arose. All of the larger case-control studies that investigated talc use and ovarian cancer (i.e., those with more than 500 cases) were population-based,[13,23,25,29,30,33,42,123,137] which should have minimized selection bias.

Recall Bias: Recall bias is another possible bias in case-control studies. Recall bias is defined as systematic error due to differences in accuracy or completeness of recall of prior events or experiences.[134] It is a concern with case-control studies because information on exposures is obtained through interviews or questionnaires completed after the cases have already been diagnosed with the disease. It is thought that people affected with a disease may have given more thought to possible causes of that disease and have more accurate recall of risk factors than a person serving as a control in the study.

A distinction is made between *recall bias*, which arises from cases recalling exposures differently than controls, and *inaccurate recall* of an exposure that is difficult to remember with precision. Recall bias, which is considered differential misclassification between cases and controls, can result in either an overestimate or underestimate of the true relative risk. Inaccurate recall that occurs to a similar degree in cases and controls is considered non-differential misclassification, and for a dichotomous outcome (e.g., ever vs. never use of talc) will typically result in an underestimate of the true relative risk. An exposure like talc use, especially when assessing use over many years, is clearly one that is subject to a certain amount of inaccurate recall. However, inaccurate recall alone would not result in the consistently increased relative risks observed in the vast majority of the case-control studies of talc use and ovarian cancer.

Therefore, recall bias, which theoretically could result in a biased estimate of the relative risk, must be considered. Situations where recall bias would be considered a particular threat to a study's validity would be: 1) the exposure of interest is one that could be considered sensitive (e.g., illicit drug use, induced abortions), 2) the study hypotheses are known to the

study subjects or interviewers, or 3) there has been considerable media attention focused on an exposure.

In regard to the first situation, genital talc use, while addressing a rather personal topic, would not be considered a particularly sensitive topic. One would not expect that women would be disinclined to report its use out of embarrassment or a desire to report what is perceived to be more socially acceptable as has been reported for exposures like induced abortion.[141]

As to the second point regarding the blinding of the interviewers and the study participants to the study hypotheses, this is standard practice in epidemiologic research. In addition, in the typical case-control study, the investigators are collecting a tremendous amount of questionnaire data to address numerous hypotheses and there is not a particular focus on a single exposure. As an example, the questionnaires from AACES and the North Carolina Ovarian Cancer study each took approximately 1 - 1.5 hours to administer and collected information on a large number of exposures including pregnancy history, contraceptive and hormone use, family history of cancer, medical history, psychosocial factors and lifestyle factors. Data were collected on factors that were expected to be associated with increased risk (e.g., family history of cancer, history of infertility, menopausal hormone use, talc use) as well as those expected to be associated with decreased risk (e.g., oral contraceptive use, pregnancies, physical activity). Given the broad range of hypotheses and the numerous exposures that the cases and controls were queried about and the fact that neither cases nor controls were told in advance of the interview about the specific topics that would be covered, it is unlikely that the women with ovarian cancer would have given more thought to their talc use resulting in substantial systematic over-reporting of talc use among cases. This is supported by studies of other cancers that used empirical data to assess the likely effect of recall bias on relative risk estimates when investigators examined numerous exposures and concluded that recall bias did not consistently lead to increased estimates of the relative risk. [142-144]

Further evidence that recall bias in case-control studies does not inevitably lead to an overestimate of the association between a risk factor and exposure comes from a recent review of meta-analyses of observational studies by Lanza et al.[145] This review analyzed a random

sample of 23 meta-analyses of observational studies addressing different exposure/disease associations published in 2013 and compared findings from case-control studies and cohort studies within individual meta-analyses to determine if conclusions from case-control studies were significantly different from those from cohort studies. The authors concluded that there was no significant difference in effect estimates between the case-control and cohort studies, suggesting that the study design did not have an important impact on the conclusions of the meta-analyses. Although recall bias *theoretically* could lead to an overestimate of the association between a risk factor and disease, the empirical evidence indicates that in practice the effect is small in most situations.

The third situation of the effect of media attention on an exposure deserves consideration as there has been reporting in the lay press in recent years about lawsuits involving talc and ovarian cancer. This concern is not relevant to the vast majority of the studies as virtually all of the data collection in the epidemiologic studies of talc and ovarian cancer occurred prior to such litigation. However one notable exception is AACES,[13] which began enrollment in 2010 and included data collected up through August, 2015. At the recommendation of the reviewer who critiqued the manuscript when it was submitted for publication, our group examined the association between talc and ovarian cancer stratified by the date of enrollment. The odds ratio for genital talc use and ovarian cancer was 1.44 for the overall study population and 1.19 for the participants interviewed before 2014. These data do give some credence to the idea that recall bias could have led to the higher odds ratios when including women interviewed during the time when there was more media attention focused on this exposure, however the fact that the association was attenuated but not eliminated when considering the full study population suggests that the association is not due entirely to recall bias.

Another way to approach the issue of whether recall bias is a likely explanation for the association between talc use and ovarian cancer is to consider whether the association was observed for other gynecologic cancers. The data are admittedly very sparse in this regard, however the only published case-control study of talc use and endometrial cancer reported an odds ratio of 0.88 (95% CI 0.68 – 1.14).[67] A study of ovarian cancer that was conducted by

several of the same investigators as the endometrial cancer study used similar methodology, was conducted in a similar timeframe (early to mid-2000s) in the same geographic region (Australia) and reported a similar prevalence of talc use in the study population. In contrast to their endometrial cancer study in which the investigators observed a non-significant inverse association with talc use, the investigators found a statistically significant increased risk for ovarian cancer associated with talc use (odds ratio=1.17, 95% CI 1.01 – 1.36).[123] While this comparison clearly needs to be interpreted cautiously because there is only a single published case-control study of talc use and endometrial cancer, it does provide evidence to suggest that the association between talc and ovarian cancer observed in most case-control studies is not due simply to recall bias.

Cohort Studies – Strengths and Weaknesses: In contrast to the case-control study, the prospective cohort study design is less susceptible to the selection bias and recall bias described above. Women who develop cancer and the comparison group are from the same population (the cohort) so the bias that could arise from improperly selecting a control group is minimized. Similarly, because the exposure information is collected before the diagnosis of cancer, one would not expect that recall of exposures would differ between the women who went on to develop cancer and those who remained free of cancer.

Despite these advantages, cohort studies do have some important disadvantages in relation to studying cancer etiology. The first is that even with large cohorts, it takes many years for a reasonable number of cancers to develop within the cohort, especially for an uncommon cancer like ovarian cancer. When considering the statistical power of a study to assess the association between an exposure and a disease, the size of the cohort is not the only driver of study power. A more critical consideration is the number of cases that develop within the cohort, which in turn is dependent on the length of follow-up of the larger cohort. Therefore, a large cohort with a relatively short duration of follow-up during which time a small number of cases developed among cohort will have low statistical power. In contrast, the total sample size of a case-control study is likely to be much smaller than a cohort study, but if it has a larger number of cases, it will have greater statistical power than the cohort study.

Among the three cohort studies included in the most recent meta-analysis,[56] the Nurses' Health Study reported 307 cases in a cohort of 78,630 women after approximately 14 years of follow-up;[34,146] the Women's Health Initiative reported 429 cases in a cohort of 61,576 women after a mean of 12.4 years of follow-up[27] and the Sister Study reported 154 cases in a cohort of 41,654 women after a mean of 6.6 years of follow-up.[24] Even with tens of thousands of women in these studies, the number of ovarian cancer cases within each cohort is smaller than the number of ovarian cancer cases in many of the case-control studies. In particular, the number of cases within the Sister Study is smaller than the number of cases in any of the case-control studies published since 1993. As described in a commentary by Narod[81], the lack of a significant overall association between ever use of talc and ovarian cancer in the cohort studies may be due to the fact that the despite the large size of the cohorts, the studies were not adequately powered to detect a relative risk of approximately 1.2.

Another limitation of cohort studies that is of greater relevance to the question of talc use and ovarian cancer is information bias related to exposure assessment. Cohort studies are typically designed to examine many different outcomes that develop within the study population over time. The Nurses' Health Study (http://www.nurseshealthstudy.org/selected-publications) and Women's Health Initiative (https://www.nhlbi.nih.gov/whi/references.htm) have reported on many different outcomes including, but not limited to, multiple types of cancer, cardiovascular diseases, fractures, gastrointestinal conditions and mental health. In contrast, case-control studies focus on a single disease, such as ovarian cancer. Because cohort studies are designed to examine diverse outcomes, the questionnaires must obtain data on risk factors that are relevant to a wider variety of diseases. To keep the questionnaire to a manageable length, a cohort study will typically query about more risk factors but in less detail than a case-control study that is focused on a single disease. This is the case with the talc questions, with the cohort studies collecting less detailed information on talc use, especially in regard to duration and frequency of use, than most of the case-control studies.

It is also worth noting that cohort studies are also subject to recall errors, especially when assessing exposures that began early in life. When the cohort studies assessed talc use, they were asking women to recall their past use of the products up to the point of interview,

similar to how exposure is assessed in the case-control studies. In the Nurses' Health Study, the cohort members were aged 36 to 61 at the time talc use was assessed in 1982, and in the Women's Health Initiative, the mean age at enrollment was 63. Because many women initiate use of talc at a young age, the study participants would have been recalling exposures over several decades, and it stands to reason that there would be some errors in recall. Therefore, in cohort studies as in case-control studies, reported talc use was subject to some degree of inaccurate recall. This likely resulted in non-differential misclassification of the exposure, which usually results in an underestimate of the true relative risk.

Another concern with exposure assessment in cohort studies that is highly relevant to the question of talc use in relation to ovarian cancer is that risk factor information can change over time. If the questionnaire data that were collected when the cohort was assembled do not include a comprehensive exposure history to that time point and are not updated over time, the information may not reflect the complete exposure history of an individual in the time before she was diagnosed with cancer. This could result in some talc users being incorrectly identified as non-users or in incorrect estimates of the duration of exposure.

Incomplete exposure assessment is a potential problem for each of the three cohort studies that have reported on talc use and ovarian cancer, however it is a particular issue for the Sister Study [24] which reported a non-significant inverse association between talc use and ovarian cancer (relative risk of 0.73, 95% CI 0.44 – 1.20). Each of the cohort studies assessed talc use at a single point in time and did not update the information at subsequent follow-up interviews. The Nurses' Health Study collected limited information on talc exposure in 1982, and did not collect additional data on talc use in subsequent questionnaires between 1982 and when the results were described in papers published in 2000 [34] and 2010. [146] Similarly, the Women's Health Initiative collected information on talc exposure when the women were enrolled into the study and did not obtain updated information during the years the cohort was followed. Therefore, any use of talc after that single exposure assessment was not captured, and there would be a certain amount of misclassification of the exposure in both the women who subsequently developed ovarian cancer and those who did not. If the misclassification was non-differential, meaning that the degree of misclassification was similar between the women

who developed ovarian cancer and those who did not, the predicted effect would be a bias towards the null.[140] In other words, non-differential misclassification of talc exposure (as a dichotomous variable) would mean that the observed relative risk was not as strong as it would have been if there had been not misclassification.

The degree of misclassification of exposure in the Sister Study [24] is apparently much greater than in the other cohort studies. Use of talc was assessed through questions about personal care products used only in the 12 months prior to enrollment, including genital talc use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap or vaginal area. This assessment is essentially a “snapshot” of talc use during a short period of time, capturing neither the cumulative use of talc up to that point nor any subsequent use of talc after the baseline interview. Not surprisingly, the reported prevalence of talc use was quite low in this study. The 14% prevalence reported in the Sister Study was markedly lower than the other two cohort studies (40.2% in the Nurses’ Health Study [34] and 52.6% in the Women’s Health Initiative [27]) as well as in nearly all of the case-control studies. In addition to underestimating the prevalence of talc use in their population, their assessment of talc only during the year prior to enrollment probably did not capture exposure during the most relevant period of the woman’s life. As the authors acknowledged in their paper, if latency (the time between exposure and diagnosis of cancer) is 15 to 20 years, the exposure assessments do not accurately reflect the period of risk. The limitations in the assessment of talc use raise serious questions about the validity of the findings from the Sister Study for this particular exposure. It is impossible to predict the direction or the magnitude of the association between talc use and ovarian cancer if the Sister Study had conducted a more complete assessment of the exposure.

A further limitation of the exposure assessment in the Nurses’ Health Study and Women’s Health Initiative is that neither assessed both the frequency and duration of use of talc. This additional limitation has ramifications for assessing dose-response gradients, which will be discussed in a later section of this report.

While cohort studies are often considered a stronger study design for assessing causal relationships between an exposure and outcome, this is not absolutely true for all exposures and outcomes. Rather than making a judgement about the quality of evidence based solely on

study design, it is important to consider study design from a more nuanced perspective and consider whether a cohort or case-control study provides the most optimal assessment of the exposure and outcome. As described above, each of the three cohort studies that has addressed talc use and ovarian cancer risk had substantial limitations in their assessment of talc use within their study population, which weakens their conclusions that talc use is not significantly associated with ovarian cancer risk.

In addition, the Sister Study,[24] which is a study that was designed primarily to examine breast cancer outcomes among women who had a sister with breast cancer, the small number of ovarian cancer cases despite the large size of the cohort and the inadequate assessment of talc exposure arguably make it a much weaker study than some of the larger, well-designed population-based, case-control studies. Notably, this study, with a relative risk estimate of 0.73 (95% CI 0.44 – 1.20) [24] could be considered an outlier as it is only one of two studies that reported a relative risk substantially less than 1, the other being Hartge's 1983 hospital-based case-control study.[49]

Uncontrolled Confounding in Observational Studies: Uncontrolled confounding is a potential concern in both case-control and cohort studies since they are observational studies. If a factor is associated with talc use *and* is a risk factor for ovarian cancer and is not accounted for in the statistical analysis, it could confound the association between talc use and ovarian cancer. In other words, if there is confounding, the increased risk observed with talc use could be due to the failure to account for the other risk factor. Vaginal douching, which was found to be associated with ovarian cancer risk in the Sister Study, was examined as a potential confounder of the association between talc use and ovarian cancer.[24] Their analyses showed that adjusting for douching using statistical modelling had a negligible effect on the association between talc use and ovarian cancer, providing no evidence of confounding. Other studies have either found an association between talc and ovarian cancer when controlling for douching [44] or found no association between douching and ovarian cancer,[49] thus the available data do not support that douching is a confounder of the association between talc and ovarian cancer. Although uncontrolled confounding is a theoretical possibility, to my knowledge, in the more

than 30 years of research on talc and ovarian cancer no such confounder has been identified that could account for the increased risk associated with talc use.

Overall, the meta-analyses indicate a high level of consistency in findings, especially from the case-control studies. Although weaker associations were observed in the cohort studies, the most recent meta-analysis did report statistically significant associations with invasive serous ovarian cancer in the cohort studies as well as in the case-control studies that reported on histologic subtype.[56] As a whole, the weaker associations observed for the cohort studies could be plausibly explained by limited methods used for talc exposure assessment, the limitations described above, including the most recent cohort study by Gonzalez, et al.,[24] which will have the predicted effect of biasing the results towards the null (i.e., showing an effect that is weaker than the true effect).

Taken as a whole, the overwhelming statistical strength of these studies, whose results are replicated over decades across a wide variety of populations and investigators, further supported by consistent meta-analysis, weighs very heavily in favor of a causal inference.

Temporality

Temporality is the only consideration that is an absolute criterion when making a judgment of causality. This criterion states that a cause (the exposure) must precede the effect (the outcome of interest) in time. Both the cohort and case-control studies that examined talc use in relation to ovarian cancer assessed talc exposure that preceded the diagnosis. In cohort studies, the questionnaire data are obtained before any women in the cohort have a diagnosis of ovarian cancer, and in the case-control studies, women with ovarian cancer are asked to report on exposures that occurred before their diagnosis and controls are asked to report on exposures that occurred in a similar time frame. Therefore, there is no question that the exposure assessment captured talc exposure that preceded the diagnosis of ovarian cancer. Nevertheless, this factor is not highly weighted; while its absence would be fatal to a causal inference, its presence is not particularly compelling support for causation.

Biological Gradient

Associations that show evidence of a biological gradient, or dose-response relationship, are considered to have stronger evidence of causality. While the inconsistencies in reported dose-response trends for talc and ovarian cancer have been noted in some meta-analyses and reviews, e.g.,[51,54] there are several considerations about this exposure that should be taken into account.

First, for an association like talc and ovarian cancer, the dose that is most relevant is the amount of talc that actually reaches the fallopian tubes and ovaries. The epidemiologic data rely on measures of external application as a surrogate of the level of exposure, not the actual exposure in the upper genital tract.

Second, there is some inherent inaccuracy in the measurement of the exposure, as the participants in most studies were asked to recall their duration and/or frequency of use over many years.

Third, the dose of talc exposure has been assessed differently across the studies. Some studies assessed only duration of use (months or years), some assessed only frequency of use (e.g., number of days per month) and some used measures of both duration and frequency to come up with a measure of total dose (estimated lifetime number of applications). The limitations of relying on duration or frequency alone as a measure of talc dose are apparent. For certain exposures, oral contraceptive use for example, duration of use is a good measure of total exposure because the pills are taken once daily. In contrast, patterns of talc exposure may be more inconsistent. Some women may use it daily, others only during their menstrual periods, others may apply it only during certain times of the year and others may have still different patterns of use. Measures of exposure based only on duration of use or only on frequency of use could result in inaccurate estimates of total exposure and obscure a dose-response relationship.

Some of the meta-analyses have cited the lack of a clear dose-response relationship as an argument against talc being a cause of ovarian cancer, and when considering measures of either years of talc use or number of applications of talc per month, there is considerable heterogeneity across studies. When considering the studies that examined dose-response associations considering both dose and frequency to estimate the total number of applications

of talc,[13,14,25,29,30,32,35,41], the majority [13,14,25,30,32] did find significant trends of higher risk with more lifetime applications of talc.

Terry, et al. [14] noted in the pooled analysis of eight case-control studies that the trend for increasing risk for non-mucinous ovarian cancers with an increasing number of genital powder applications was significant when non-users were included in the analysis, but the trend was not significant when the analysis was restricted to ever users. The authors therefore concluded that the significant trend was largely due to the comparison of women who had ever used talc versus those who had never used it, suggesting that the dose-response relationship was not a simple linear increase in risk with greater exposure to talc.

While there is evidence of a dose response relationship in the majority of the studies that considered both frequency and duration of use (i.e., total number of applications), these observations are less consistent than the overall association between talc and ovarian cancer. There are several possible reasons why not all studies observed dose-response relationships, even when an overall association was observed in the study. First, there is likely to be greater inaccuracy in the recall of duration of use as compared to ever/never use, which would tend to obscure a dose-response relationship. Second, when “ever-users” were stratified into duration of use categories, it often resulted in strata with small numbers of women, resulting in less stable relative risk estimates within the duration categories. Third, as noted by Terry, et al.[14], the dose-response relationship may not be a simple linear trend. In many of the studies, even the women in the lowest exposed category had hundreds of episode of talc exposure. Because there could have been considerable exposure even among the women in the “low” exposure categories, greater exposure may not have resulted in substantially increased risk and thus a linear trend may not have been apparent.

Overall, biological gradient was given lesser weight in my assessment of the literature, based on: 1) some of the studies that assessed a dose-response relationship evaluated only duration or frequency of use and not total number of applications, 2) duration and frequency of use are subject to more misclassification than ever use of talc, 3) small sample sizes within strata lead to unstable estimates, and 4) there is the possibility of a non-linear dose-response relationship. Nonetheless, even with these limitations, there was still evidence of a dose-

response relationship in the majority of studies that evaluated it based on the total number of applications.

Biologic Plausibility

Biological plausibility refers to whether there is a reasonable biological mechanism through which the exposure could lead to the disease. Hill is quick to point out that biological plausibility depends on the current state of scientific knowledge. Specifically, Hill wrote "It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day." It is clear that from these statements that the consideration of biological plausibility does not require that that there is a *proven* biological mechanism to make a judgment of causality between an exposure and disease. Therefore, for this Hill consideration, a scientist looks for biological evidence that might explain the associations that are observed in the epidemiologic studies. In other words, one has to see whether the observed association "makes sense" biologically. In this case, I have considered both clinical plausibility and biological plausibility. Both of these show that the association seen in the epidemiologic studies "makes sense."

It is probably safe to say that our understanding of the complex biological processes that lead from exposure to disease is incomplete for all cancers. In some instances, the precise biological mechanisms by which an exposure leads to disease remain unclear and in others, some mechanisms are well-established but there is not a complete understanding of why some exposed individuals develop the disease and others do not. An example of the former is alcohol consumption as a cause of breast cancer. While alcohol is considered by IARC to be an established cause of breast cancer, [128] recent publications still describe the association as one in which the exact biological pathways are unclear, even though several possible mechanisms have been hypothesized (i.e., metabolism to acetaldehyde or effects on estrogen levels).[147,148] An example of the latter is smoking and lung cancer. Mechanisms of carcinogenesis from constituents of tobacco smoke have been well-described,[149] however it remains unclear as to why some smokers are more susceptible to developing lung cancer. In short, it is important to

recognize that biological plausibility depends on the current state of knowledge and may evolve over time as new evidence emerges.

When considering the likelihood of talcum powder products causing ovarian cancer, there is robust data that leads to the conclusion that there are biologically plausible mechanisms by which this exposure could lead to ovarian cancer. Specifically, 1) talcum powder products can migrate from the perineum through the genital tract to the ovaries and fallopian tubes, 2) talcum powder products can become imbedded in the ovarian tissue; 3) talcum powder products can induce an inflammatory response, and 4) the inflammatory response can result in increased oxidative stress and expression of cytokines, mutagenesis, and cell proliferation.

Pathology studies have demonstrated that particles may ascend the female genital tract from the vagina to the fallopian tubes and ovaries,[150,151] and talc particles have been identified in ovarian tissue.[71,76,78,79] In fact, the FDA's 2014 response to the Citizen's Petition requesting a cancer warning label on cosmetic talc products states that "the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable".[152] Therefore, it is highly plausible that application of talcum powder products to the genital area can result in exposure to the ovaries.

It is also plausible that inhalation of talc products could also be a route of exposure leading to cancer. Studies of asbestos exposure indicate that inhalation of asbestos fibers can result in exposures to the peritoneal tissue, through transport through the lymphatic system and/or blood.[153-155] There is strong evidence that such exposure can result in cancer, most notably mesothelioma. Inhalation of talcum powder products could result in similar peritoneal exposure.

Given the evidence that external application of talcum powder products can reach the ovaries either through upward migration through the genital tract or through inhalation and subsequent transport through the lymphatic system and/or blood, there are plausible biological pathways by which talc could lead to the development of ovarian cancer.

It is well-established through several lines of evidence that talc can cause inflammation. The inflammatory properties of talc are exploited for clinical use in talc pleurodesis, a treatment

for malignant pleural effusions or pneumothorax that involves instillation of talc into the pleural space.(https:www.uptodate.com/contents/talc-pleurodesis) The resultant inflammation and fibrosis result in adhesion of the layers of the pleura, closing the pleural space. The inflammatory properties of talc are also evident in that chronic or acute exposure to talc through inhalation which can result in pulmonary talcosis, a chronic inflammation of the lower respiratory tract.[156,157] Animal studies also confirm that talc causes inflammation, as experiments in rats treated with intra-vaginal or perineal talc showed inflammatory changes in the genital tract.[70] Although neoplastic changes were not observed in this experiment, this could be explained by the small number of animals (n=7) in each group or the duration of the experiment (3 months).

Inflammation has been identified as one of the hallmarks of cancer, with both extrinsic and intrinsic pathways described.[158,159] Talc would be characterized as being involved in an extrinsic pathway, in which an exposure or condition results in chronic, non-resolving inflammatory responses. Chronic inflammation can lead to a cascade of cellular events that could result in damage to DNA, increased cell division and generation of inflammatory mediators.

Recent work by Saed, Fletcher, et al. [160,161] describes the role of oxidative stress in the pathogenesis of ovarian cancer and the effects of talc on the oxidative state of ovarian cancer cell lines. Oxidative stress results when the balance between oxidant and anti-oxidant enzymes and molecules in cells is altered, resulting in an excess of reactive oxygen species or reactive nitrogen species. Oxidative stress, which can result from numerous factors including exposure to carcinogens, infection and chronic inflammation, has been shown to affect the initiation, promotion and progression of several types of cancer. Saed, et al. have reported that talc can generate a pro-oxidant state in both normal ovarian epithelial cells and ovarian cancer cells. Exposure to talc resulted in an increase in mRNA levels of certain pro-oxidant enzymes and a decrease in the mRNA of several anti-oxidant enzymes, suggesting a possible cellular mechanism by which exposure to talc could contribute to the development of ovarian cancer.

There is also evidence in the medical literature that talc products contain additional constituents that are known ovarian carcinogens, particularly asbestos.[162-166]

Asbestos is one of the most established carcinogens in our environment, and is associated with a variety of cancers including mesothelioma, lung, larynx and ovarian.[167,168] IARC has stated that "a causal association between exposure to asbestos and cancer of the ovary was clearly established," based on strongly positive cohort mortality studies of women with occupational exposure to asbestos as well as studies of women with environmental exposure to asbestos.[169] The Occupational Safety and Health Administration has stated that "there is no safe level of asbestos exposure for any type of asbestos fiber" and that asbestos exposures as short as a few days have resulted in cancer (mesothelioma), indicating that even low levels of exposure may be carcinogenic. (https://www.osha.gov/SLTC/asbestos/)

Although it has been often stated that talc products manufactured after 1976 are asbestos-free, evidence from published scientific reports, [57,162] analyses performed on samples manufactured and packaged at different time points after 1976,[170-173] and internal documents and testimony from the defendants demonstrate that statement is inaccurate.[174,175] There is evidence that products manufactured after 1976 are not asbestos-free. Studies from Longo, et al. show that talc products can contain asbestos and talc containing asbestiform fibers (e.g., talc occurring in a fibrous habit).[170,171] Therefore it is reasonable to conclude that women who regularly used talc products, both before and after 1976, were likely exposed to asbestos and talc containing asbestiform fibers through their use of these products.

Analyses of talcum powder products also demonstrate the presence of other constituents such as chromium and nickel which are well established carcinogens, and cobalt which is considered a possible carcinogen.[169,174] I have also reviewed a report analyzing the 150+ known fragrance ingredients in talcum powder products, many of which have been determined harmful to humans.[176] The presence of these substances provide further evidence that exposure to talc products could result in cancer

It is also plausible that even among women recently diagnosed with ovarian cancer, exposure to the pre-1976 talc products, which are generally understood to have contained asbestos and talc containing asbestiform fibers, increased their risk for ovarian cancer. It is well-established that many cancer risk factors have a long latency, which the National Cancer Institute defines as "the time that passes between being exposed to something that can cause

disease and having symptoms". Numerous examples of cancer risk factors with prolonged latency periods exist. For example, lung cancer typically is not diagnosed among cigarette smokers for several decades after initial exposure [177] and having severe sunburns during childhood is a risk factor for melanoma,[178] which has a median age of diagnosis of 63 years. [135]

It has also been reported that the latency period between exposure to asbestos and mesothelioma (the cancer most strongly linked to asbestos exposure), ranges from 15 to more than 70 years.[179,180] The median latency has been estimated at 22 to 32 years, with longer latency periods estimated for women than for men.[179,180] Thus, it is not unreasonable to conclude that exposure to talc products early in a woman's life could result in ovarian cancer decades later.

Further, other established risk factors for ovarian cancer also demonstrate long latency periods. Oral contraceptive use and history of pregnancy are two of the factors that are most consistently reported in association with ovarian cancer (both of which reduce risk). Although, these are "exposures" that typically occur when women are in their teens, twenties or thirties, the median age of diagnosis of ovarian cancer is 61 years, suggesting that events and exposures from early in a woman's reproductive life can influence her risk for ovarian cancer decades later.

The totality of this evidence indicates that there are plausible biological pathways by which use of talc products could lead to ovarian cancer. There is clear evidence that external applications of these products can result in exposure to the ovaries, through upward migration through the genital tract or inhalation exposure. Once exposed, there are plausible biological mechanisms, by which talc itself or constituents of the talcum powder product could lead to carcinogenic transformation of ovarian cells. This includes credible evidence that talc products contain asbestos fibers, a known ovarian carcinogen, regardless of whether they were manufactured before or after 1976. While it is likely that advances in scientific knowledge may further refine our understanding of how talc exposure can lead to ovarian cancer, our current knowledge is adequate to conclude that there are plausible biological pathways leading from talc exposure to ovarian cancer.

I have considered the biologic plausibility that would support and detract from the hypothesis that talcum powder products can cause ovarian cancer. The more persuasive evidence is that talc can migrate to the ovaries through the genital tract and become imbedded in ovarian tissue. It is also plausible that talc could reach the peritoneal cavity through an inhalation route. Regardless of the route of exposure, it is clear that talcum powder products, including constituents like asbestos and fibrous talc, may cause an inflammatory response and oxidative stress that could lead to cell damage. These biologically plausible mechanisms are a persuasive explanation for the consistent increased risk we have observed in the epidemiologic studies. *Simply put, the observed association "makes sense" biologically.* Along with consistency and strength, I considered this a strong factor favoring a causal inference.

Specificity

As described by Hill,[121], if specificity exists between an exposure characteristic and disease, it provides strong evidence of causality. However, he also stated that "one-to-one relationships are not frequent …multi-causation of disease is generally more likely that single causation". Clearly, ovarian cancer has multiple causes, with talc exposure among many known risk factors. From the standpoint of there being a "one-to-one relationship" between talc and ovarian cancer, there is not a high level of specificity. However, given that talcum powder products are particularly associated with epithelial ovarian cancer, especially serous ovarian cancer, it does support that it is a fairly specific relationship. This aspect was given only modest weight, because talc is one of many possible causes of ovarian cancer.

Coherence

It is recognized that the plausibility depends on the current state of biological knowledge. Knowledge of the biological mechanisms for ovarian carcinogenesis (and virtually any other disease) is incomplete and will continue to evolve as further research continues. Coherence, as described by Hill, means that, even if the knowledge of biology of the disease is not well-defined, the "data should not seriously conflict with the generally known facts of the natural history and biology of the disease".[121] Given the current state of knowledge of ovarian

carcinogenesis, the postulated mechanisms by which talc exposure leads to ovarian cancer do not conflict with the current state of knowledge on ovarian carcinogenesis. This aspect was given considerable weight as it is important that the overall evidence fit together in a coherent manner. Taking into account the plausible pathways by which talc products could reach the target tissue, the expected latency period between exposure and disease, and biological mechanisms that are consistent with our knowledge of carcinogenesis, the data are consistent with the natural history and biology of ovarian cancer.

Experiment

As described above, the epidemiologic data on talc use and ovarian cancer are from observational studies, therefore there are no clear cut experimental data on which a causal assessment can be made. Hill acknowledged that experimental data are often not available for the exposure/disease associations under study, but in some circumstances, experimental or semi-experimental evidence is available.[121] For example, if a preventive action is taken to remove the exposure and the incidence of disease declines, there is strong support for a causal relationship. No such experimental evidence is available for talc use and ovarian cancer.

Analogy

The final viewpoint defined by Hill [121] is analogy, whereby evidence of an association with one risk factor would suggest that a similar risk factor could also plausibly be associated with the disease. Because this viewpoint is rather vague, it is often not incorporated into causal assessments. Nevertheless, while I did not weight it heavily, the similarity between asbestos and asbestiform talc – both of which are widely accepted as causing ovarian cancer – is supportive of this viewpoint.

Conclusion

Epidemiologic evidence linking genital talc use to ovarian cancer has been accruing since 1982.[50] As I evaluated this evidence, I considered the results from individual studies with different designs (case-control and cohort) as well as meta-analyses and a pooled analysis of

multiple case-control studies. In my evaluation of the data, I considered the strengths and weaknesses of individual studies, recognizing that there are advantages and disadvantages of both case-control and cohort studies for evaluating talc as a risk factor for ovarian cancer. I used the Bradford Hill framework as a guide for making my weight of the evidence assessment of whether there is evidence for a causal association between talc use and ovarian cancer.

The epidemiologic evidence I evaluated was derived from more than two dozen studies conducted in many different settings. The vast majority of studies reported relative risks or odds ratios greater than one, indicating that women with ovarian cancer were more likely to have used talc products than women without ovarian cancer. Meta-analyses, which combine findings across multiple studies to come up with an overall estimate of risk that is more statistically robust, have consistently reported that there is a statistically significant increased risk for ovarian cancer among women who reported genital talc use. While meta-analyses have noted that the relative risk estimates from case-control studies have been larger than from cohort studies, limitations in all of the cohort studies could explain the weaker associations observed in these studies. It is also noteworthy that the most recent meta-analysis [56] reported significantly increased risks for invasive serous ovarian cancer, which is the most common subtype as well as the one with the worst prognosis, in both cohort and case-control studies.

The epidemiologic studies that have examined talc use in relation to ovarian cancer risk have been conducted in very diverse populations, both within and outside the United States and in women of different race/ethnicities. The consistency of the findings across populations adds credibility to the findings of increased risk of ovarian cancer among talc users.

The relative risk estimates in most studies and the summary relative risk estimates from the meta-analyses are of a magnitude (~1.25-1.30) that is comparable to other common exposures that are causally related to cancer (e.g., passive smoke exposure and lung cancer, oral contraceptive use and breast cancer, menopausal estrogen use and breast cancer, residential radon exposure and lung cancer). Additional evidence supportive of talc being an ovarian cancer risk factor are biologically plausible mechanisms based on inflammation pathways, oxidative stress and the presence of asbestos, asbestiform talc, and other known

carcinogens in talcum powder products. Evidence of a dose-response relationship exists in many of the studies that considered both duration and frequency of exposure.

Based on the evidence in total, it is my opinion with a reasonable degree of scientific certainty that use of talcum powder products can cause ovarian cancer. I reserve the right to modify or refine my opinions based on additional scientific evidence that may emerge on this topic.

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147. JNJ000294461
148. JNJ000346006-JNJ000346014
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150. JNJ000375383-JNJ000375384
151. JNJ000526231-JNJ000526676
152. JNJ000637879-JNJ000637881
153. JNJAZ55_000003357
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159. JNJNL61_000063473
160. JNJTALC000090136
161. MBS-CRE000271
162. PFE-HUG00007079
163. PFE-HUG00007124
164. PFE-HUG00007194
165. WCD000254-WCD000255

EXHIBIT A

Duke University Medical Center
Curriculum Vitae

Date Prepared: October 2018

Patricia Gripka Moorman, M.S.P.H., Ph.D.

Primary academic department:	Department of Community and Family Medicine Duke University Medical Center
Present academic rank and title:	Professor with tenure, September 2014
Date and rank of first Duke faculty appointment:	July 1, 2000, Assistant Professor
Medical licensure:	N/A
Date of birth:	December 19, 1957
Place of birth:	Kansas City, Kansas, USA
Citizen of:	United States of America

EDUCATION

	Institution	Year	Degree
High School	Bishop Ward High School Kansas City, KS	1975	Diploma
College	University of Kansas Lawrence, KS	1980	B.S. with distinction, Pharmacy
Graduate School	University of North Carolina – Chapel Hill Chapel Hill, NC	1989	M.S.P.H., Epidemiology
	University of North Carolina – Chapel Hill Chapel Hill, NC	1993	Ph.D., Epidemiology

PROFESSIONAL TRAINING AND ACADEMIC CAREER

Institution	Position/Title	Dates
Shalinsky Drugs, Kansas City, KS	Pharmacist	1980-1981
Community Pharmacy, Wrentham, MA	Pharmacist, Manager	1981-1982
Revco Drugs, Durham/Raleigh, NC	Pharmacist, Manager	1983-1993
Department of Epidemiology University of North Carolina - Chapel Hill	Graduate Research Assistant Teaching Assistant	1987-1993
Burroughs Wellcome Research Triangle Park, NC	Epidemiology Research Associate Summer Intern	1988
Department of Epidemiology Lineberger Comprehensive Cancer Center University of North Carolina - Chapel Hill	Research Assistant Professor	1994-1996
Dept. of Epidemiology and Public Health Yale Comprehensive Cancer Center Yale University School of Medicine New Haven, CT	Associate Research Scientist	1997-2000
Department of Epidemiology University of North Carolina - Chapel Hill	Adjunct Assistant Professor Adjunct Associate Professor	2000-2005 2005-present
Dept. of Community and Family Medicine Duke University Medical Center	Assistant Professor Associate Professor (non-tenured) Associate Professor (tenured) Professor (tenured) Clinical Research Unit Director (formerly Site-Based Research Director)	2000-2004 2004-2008 2008-2014 2014-present 2009-present

PUBLICATIONS

Refereed Publications

1. Aldrich TE, Vann D, **Moorman PG**, Newman B. Rapid reporting of cancer incidence in a population-based study of breast cancer: one constructive use of a central cancer registry. *Breast Cancer Res Treat.* 1995; 35: 61-64.
2. Newman B, **Moorman PG**, Millikan R, Qaqish BF, Geradts J, Aldrich TE, Liu ET. The Carolina Breast Cancer Study: integrating population-based epidemiology and molecular biology. *Breast Cancer Res Treat.* 1995: 51-60.
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case-control study with three groups of controls. *Cancer Epidemiol Biomarkers Prev*. 2009; 18:1232-8. (PMCID: PMC2700947)

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114. DeBono NL, Robinson WR, Lund J, Tse CK, **Moorman PG**, Olshan AF, Troester MA. Race, menopausal hormone therapy and invasive breast cancer in the Carolina Breast Cancer Study. *J Women's Health* 2018; 27: 3770386.

115. Abbott SE, Camacho F, Peres LC, Alberg AJ, Bandera EV, Bondy M, Cote ML, Funkhouser E, **Moorman PG**, Peters ES, Qin B, Schwartz AG, Barnholtz-Sloan J, Terry P, Schildkraut JM. Recreational physical activity and survival in African American women with ovarian cancer. *Cancer Causes Control* 2018; 29: 77-86.

116. Peres LC, Risch H, Terry KL, Webb PM, Goodman MT, Wu AH, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, Funkhouser E, **Moorman PG**, Peters ES, Schwartz AG, Terry PD, Manichaikul A, Abbott SE, Camacho F, Jordan SJ, Nagle CM, Australian Ovarian Cancer Study Group, Rossing MA, Doherty JA, Modugno F, Moysich K, Ness R, Berchuck A, Cook L, Le N, Brooks-Wilson A, Sieh W, Whittemore A, McGuire V, Rothstein J, Anton-Culver H, Ziogas A, Pearce CL, Tseng C, Pike M, Schildkraut JM, on behalf of the African American Cancer Epidemiology Study and the Ovarian Cancer Association Consortium. Racial/ethnic differences in the epidemiology of

ovarian cancer: A pooled analysis of 12 case-control studies. *Int J Epidemiol* 2017; 47: 460-472.

117. Mills AM, Peres LC, Meiss A, Ring KL, Modesitt SC, Abbott SE, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy ML, Cote ML, Funkhouser E, **Moorman PG**, Peters ES, Schwartz AG, Terry PD, Schildkraut JM. Targetable immune regulatory molecule expression in high-grade serous ovarian carcinomas in African-American women: a study of PD-L1 and IDO in 112 Cases from the African American Cancer Epidemiology Study (AACES), *Int J Gynecol Pathology* 2018, in press.

118. Freedman JA, Wang Y, Li X, Liu H, **Moorman PG**, George DJ, Lee NH, Hyslop T, Wei Q, Patierno SR. Single nucleotide polymorphisms of stemness pathway genes predicted to regulate RNA splicing, microRNA and oncogenic signaling are associate with prostate cancer survival. *Carcinogenesis* 2018; 39: 879-888.

119. Anderson RT, Peres LC, Camacho F, Bandera EV, Funkhouser E, **Moorman PG**, Paddock LE, Peters ES, Abbott SE, Alberg AA, Barnholtz-Sloan J, Bondy M, Cote ML, Schwartz AG, Terry P, Schildkraut JM. Individual, social and societal correlates of Health-Related Quality of Life among African-American survivors of ovarian cancer: results from the AACES Study. *J Women's Health*, 2018, in press.

120. Park HK, Schildkraut JM, Alberg AJ, Bandera EV, Barnholtz-Sloan JS, Bondy M, Crankshaw S, Funkhouser E, **Moorman PG**, Peters ES, Terry P, Wang F, Ruterbusch JJ, Schwartz AG, Cote ML. Benign gynecologic conditions are associated with ovarian cancer risk in African-American women: a case-control study. *Cancer Causes Control*, 2018, in press.

121. **Moorman PG**, Barrett NJ, Wang F, Alberg AA, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, Funkhouser E, Kelemen L, Peres LC, Peters ES, Schwartz AG, Terry P, Crankshaw S, Abbott SE, Schildkraut JM. Effect of cultural, folk and religious beliefs and practices on delays in diagnosis in ovarian cancer in African American women. *J Women's Health*, 2018, in press.

122. Qian D, Liu H, Wang X, Ge J, Luo S, Patz EF Jr, **Moorman PG**, Su L, Shen S, Christiani DC, Wei Q. Potentially functional genetic variants in the complement-related immunity gene-set are associated with non-small cell lung cancer survival. *Int J Cancer* 2018, in press.

Letters

1. **Moorman PG**. Letter re: Breast cancer risk factors. *Drug Topics*. 2002; 146: 16.

2. **Moorman PG**. Letter re: Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk. *JAMA*. 2004; 292: 1426.

3. Schildkraut JM, **Moorman PG**, Calingaert B, Berchuck A. Letter re: Cyclin E overexpression relates to ovarian cancer histology but not to risk factors. *Cancer Epidemiol Biomarkers Prev*. 2008; 17: 1841-2.

4. **Moorman PG**. Letter re: Age at Menopause: Imputing age at menopause for women with a hysterectomy with application to risk of postmenopausal breast cancer. *Annals Epidemiol*. 2011; 21: 797.

5. Myers ER, **Moorman P**, Sanders GD. Response re: Breast cancer screening: benefit or harm? *JAMA* 2016; 315: 1402-3.

6. Trabuco EC, **Moorman PG**, Cliby WA. In reply re: Association of ovary-sparing hysterectomy with ovarian reserve. *Obstet Gynecol* 2016; 128: 655-6.

Book Chapters and Invited Papers

1. **Moorman PG**, Hames CG, Tyroler HA. Socioeconomic status and morbidity and mortality in hypertensive blacks. In Brest AN and Saunders E (eds): *Cardiovascular Clinics: Cardiovascular Diseases in Blacks*. FA Davis Company, Philadelphia, 1991, 179-93.

2. **Moorman PG**, Hulka BS. Menopausal hormones and the risk of breast cancer. *Endocrinologist.* 1992; 2: 189-94. (Article was awarded annual editorial prize by journal.)

3. Hulka BS, **Moorman PG**. Breast cancer: Hormones and other risk factors, *Maturitas.* 2001; 38: 103-13.

4. **Moorman PG**, Terry PD. Dairy products and breast cancer. 2003. United Kingdom Dairy Council. (Invited paper)

5. **Moorman PG**, Berchuck A. Comment on: Hormone replacement therapy does not increase risk for ovarian cancer in women with BRCA mutations. *North American Menopause Society First to Know*. Feb. 15, 2006. www.menopause.org/news.html.

6. **Moorman PG**, Hamilton RJ. Statins and cancer risk: what do we know and where do we go from here? *Epidemiology.* 2007; 18: 194-6. (Invited paper)

7. Hulka BS, **Moorman PG**. Breast cancer: hormones and other risk factors. *Maturitas.* 2008; 61: 203-213.
   (Republished 2001 article of same title in an issue of the journal's top 10 downloaded articles for the period 2000-2008).

8. **Moorman PG**. Ovarian failure after pre-menopausal hysterectomy. *European Obstetrics & Gynecology*. 2012; 7: 35-8. (Invited paper)

9. **Moorman PG.** Genetic markers for ovarian cancer risk: are we close to seeing a clinical impact? *Personalized Medicine.* 2012; 9: 565-7. (Invited paper)

10. **Moorman PG.** Should women at high risk for cancer use oral contraceptive pills? *Personalized Medicine*. 2015, 12: 533-5. (Invited paper)

Technical Reports

1. **Moorman PG**, Goldstein K, Coeytaux R, Myers ER, Strauss J, Van Houtven C, Shepherd-Banigan M, Brancu M, Von Isenberg M, Van Noord M, Conklin J, Lallinger K, Schmidt R, McBroom Brooks A, Sanders-Schmidler G. Topic Brief: Nutritional needs of older women. Prepared for Office of Women's Health and Agency for Healthcare Research Quality (AHRQ), 2017.

2. Myers ER, Strauss J, Van Houtven C, Goldstein K, Shepherd-Banigan M, Brancu M, **Moorman PG**, Coeytaux R, Von Isenberg M, Van Noord M, Conklin J, Lallinger K, Schmidt R, McBroom Brooks A, Sanders-Schmidler G. Topic Brief: Maternal Health. Prepared for Office of Women's Health and Agency for Healthcare Research Quality (AHRQ), 2017.

3. Strauss J, Brancu M, Myers ER, Anderson S, Van Houtven C, Goldstein K, Shepherd-Banigan M, **Moorman PG**, Coeytaux R, Von Isenberg M, Van Noord M, Conklin J, Lallinger K, Schmidt R, McBroom Brooks A, Sanders-Schmidler G. Topic Brief: Women's Mental Health. Prepared for Office of Women's Health and Agency for Healthcare Research Quality (AHRQ), 2017.

4. Goldstein K, Coeytaux R, Myers ER, Strauss J, Van Houtven C, Shepherd-Banigan M, Brancu M, **Moorman PG**, Von Isenberg M, Van Noord M, Conklin J, Lallinger K, Schmidt R, McBroom Brooks A, Sanders-Schmidler G. Topic Brief: Girls' Health and Obesity. Prepared for Office of Women's Health and Agency for Healthcare Research Quality (AHRQ), 2017.
5. Shepherd-Banigan M, Van Houtven C, Brancu M, Goldstein K, **Moorman PG**, Strauss J, Coeytaux R, Von Isenberg M, Van Noord M, Conklin J, Lallinger K, Schmidt R, McBroom Brooks A, Myers ER, Sanders-Schmidler G. Topic Brief: Family Caregivers for Older Adults. Prepared for Office of Women's Health and Agency for Healthcare Research Quality (AHRQ), 2017.

Non-authored Publications (acknowledged for contributions)

1. Newman B, Millikan RC, King M-C. Genetic epidemiology of breast and ovarian cancers. *Epidemiol Rev*. 1997; 19: 69-79.
2. Millikan R, Pittman G, Tse C-K, Savitz DA, Newman B, Bell D. Glutathione S-transferases M1, Ti, and P1 and breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2000; 9: 567-73.
3. Krajcik RA, Massardo S, Orentreich N. No association between serum levels of tumor necrosis factor-α (TNF- α) or the soluble receptors sTNFR1 and sTNFR2 and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2003; 12: 945-6.
4. Trivers KF, Stewart SL, Peipins L, Rim SH, White MC. Expanding the public health research agenda for ovarian cancer. *J Womens Health*. 2009; 18: 1299-305.
5. Soubry A, Il'yasova D, Sedjo R, Wang F, Byers T, Rosen C, Yashin A, Ukraintseva S, Haffner S, D'Agostino R Jr. Increase in circulating levels of IGF-1 and IGF-1/IGFBP-3 molar ratio over a decade is associated with colorectal adenomatous polyps. *Int J Cancer*. 2012; 131: 512-7.

Presentations and Published Abstracts (selected)

Moorman PG, Newman B, Butler LM, Ostermeyer EA, Friedman LS, Millikan RC, Liu ET, King MC. Inherited susceptibility at BRCA1 in a population-based sample. Society for Epidemiologic Research, Boston, MA, June 1996

Rockhill B, Newman B, **Moorman P**, Millikan R, Weinberg C. Summary attributable fraction and breast cancer risk factors. Society for Epidemiologic Research, Boston, MA, June 1996.

Furberg H, Newman B, **Moorman P**, Millikan R. Lactation and breast cancer risk. Society for Epidemiologic Research, Edmonton, Alberta, Canada, June 1997.

Marcus PM, Newman B, Millikan RC, **Moorman PG**, Baird DD, Sternfeld B, Qaqish B. The association of adolescent body mass index (BMI) and physical activity with breast cancer risk. Society for Epidemiologic Research, Edmonton, Alberta, Canada, June 1997.

Huang WY, Newman B, Millikan RC, Schell MJ, **Moorman PG**. Hormone-related factors and risk of breast cancer by estrogen receptor and progesterone receptor status. Society for Epidemiologic Research, Chicago, MD, 1998.

Hall IJ, Newman B, Millikan RC, **Moorman PG**. Evaluating body size and breast cancer risk among black women. Society for Epidemiologic Research, Chicago, MD, 1998.

Marcus PM, Newman B, Millikan RC, Baird DD, **Moorman PG,** Qaqish B. Breast cancer epidemiology: the case for adolescent exposures. Society for Epidemiologic Research, Baltimore, MD, 1999.

Moorman PG. Menopausal hormones and risk of breast cancer. Carolina Breast Cancer Study Participant Symposium, Chapel Hill, NC, April 2000

Moorman PG, Jones BA, Millikan RC, Hall IJ, Newman B. Race, anthropometric factors, and stage at diagnosis of breast cancer. Society for Epidemiologic Research, Seattle, WA, June 2000.

Hall IJ, Newman B, Millikan RC, **Moorman PG**. Comparative analysis of breast cancer risk factors among African-American women and white women. Congress of Epidemiology, Toronto, Ontario, Canada, June 2001.

Moorman PG, et al. Nuts and bolts of field studies: things they didn't teach you in school. Congress of Epidemiology, Toronto, Ontario, Canada, June 2001. (Invited talk)

Moorman PG, Calingaert B, Vine M, Halabi S, Berchuck A, Schildkraut JM. Comparison of two methods for calculating lifetime ovulatory cycles. Congress of Epidemiology, Toronto, Ontario, Canada, June 2001.

Plummer P, Jackson S, Konarski J, Mahanna E, Dunmore C, Regan G, Mattingly D, Parker B, Williams S, Andrews C, Vannapppagari V, HallS, Deming S, Hodgson E, **Moorman P**, Newman B, Millikan R. Making epidemiologic studies responsive to the needs of participants and communities: the Carolina Breast Cancer Study experience. Conference on Breast Cancer and Environmental Mutagens, Research Triangle Park, NC, September 2001.

Moorman PG. Population-based study of breast cancer among African-American and White women in North Carolina. North Carolina Central University, Durham, NC, January 2003. (Invited talk)

Moorman PG. Medication use and breast cancer risk. Psychiatry and Behavioral Sciences Grand Rounds, Memorial Sloan-Kettering Cancer Center, New York, NY, March 2003. (Invited talk)

Sansbury L, Millikan R, Schroeder J, **Moorman P**, North K, Sandler R. Use of non-steroidal anti-inflammatory drugs, cyclooxygenase-2 Val411Ala polymorphism and association with colon cancer in a population-based study of African Americans and whites. 3rd Annual AACR International Conference, Seattle, WA, October 2004.

Schildkraut JM, Berchuck A, Murphy S, Marks J, **Moorman P**, Calingaert B, Halabi S. Trinucleotide repeat polymorphisms in the androgen receptor gene and risk of ovarian cancer. 3rd Annual AACR International Conference, Seattle, WA, October 2004.

Moorman PG, Sesay J, Nwosu V, Millikan R. Non-steroidal anti-inflammatory drugs, COX2 polymorphism and breast cancer: a study of gene-environment interactions. Triangle Cancer and Disparities Symposium, North Carolina Central University, Durham, NC, March 2005.

Moorman PG. Racial disparities in breast cancer: problem or opportunity? Johnson C. Smith University, Charlotte, NC, September 2005. (Invited talk)

Trivers K, Gammon M, Abrahamson P, Lund MJ, Kaufman J, **Moorman P**, Cai JW, Porter P, Brinton L, Eley JW. Reproductive factors and breast cancer survival in women less than 55 years of age. 4th Annual Conference on Frontiers in Cancer Prevention Research, Baltimore, MD, November 2005.

Moorman PG. The role of epidemiology in the drug development process. University of Ferrara, Ferrara, Italy, May 2006. (Invited talk)

Moorman PG. Racial disparities in breast cancer: risk factors through survival. Women's Health Research Symposium - Untying the Pink Ribbon: Advances in Breast Cancer. University of Maryland School of Medicine. Baltimore, MD, March 2008. (Invited talk)

Moorman PG, JM Schildkraut JM, ES Iversen ES, ER Myers ER, M Gradison M1, N Warren-White N, F Wang. Weight gain after pre-menopausal hysterectomy. Society for Epidemiologic Research, Chicago, IL, June 2008.

Moorman PG. Non-steroidal anti-inflammatory drugs (NSAIDs) as chemopreventives for cancer: are they ready for prime time? Genetics and Environmental Mutagenesis Society 26th Annual Fall Meeting. Research Triangle Park, NC, October 2008. (Invited talk)

Moorman PG. Introduction to cancer epidemiology. Osher Lifelong Learning Institute lecture series. Chapel Hill, NC, September 2009. (Invited talk)

Moorman PG. Challenges of epidemiologic research in the genomic era: the example of ovarian cancer. Environmental Mutagen Society Annual Meeting, St. Louis, MO, October 2009 (Invited talk)

Moorman PG. Epidemiology in clinical research: beyond randomized controlled trials. Duke University Health System Clinical Education and Professional Development Series, Durham, NC, January 2010. (Invited talk)

Moorman PG. Epidemiology in clinical research: beyond randomized controlled trials. Association of Clinical Research Professionals, Durham, NC, June 2010. (Invited talk)

Moorman PG. The role of epidemiology in understanding disparities in breast cancer. Duke Oncology Symposium – Advances in Surgical and Treatment Options for Breast and Colorectal Cancer. Raleigh, NC, May 2011. (Invited talk)

Østbye T, **Moorman P**. Measurement dilemmas: validity, reliability and messy data. Family Medicine Research Seminar Series, Duke University Medical Center, December 2011.

Moorman P, Østbye T. Research that can tell you something: internal and external validity in study design. Family Medicine Research Seminar Series, Duke University Medical Center, November 2011.

Myers ER, Havrilesky LJ, Gierisch J, **Moorman PG**, Dinan MA, Coeytaux R, Urrutia RP, Lowery WJ, Hasselblad V, McBroom AJ, Sanders GD. Using net benefits and acceptability curves to quantify uncertainty about tradeoffs between harms and benefits of oral contraceptives. Society for Medical Decision Making, Phoenix, AZ, October 2012.

Myers ER, Havrilesky LJ, Gierisch J, **Moorman PG**, Dinan MA, Coeytaux R, Urrutia RP, Lowery WJ, Hasselblad V, McBroom AJ, Sanders GD. Net effects of current patterns of oral contraceptive use on potentially fatal outcomes in the United States. Society for Medical Decision Making, Phoenix, AZ, October 2012.

Stouder A, Melcher B, Morgan PA, **Moorman PG**, Lin L, Stem J. Satisfaction Guaranteed? An Analysis of Lecturer Characteristics Associated with Physician Assistant Student Satisfaction. Physician Assistant Education Association Annual Education Forum, Seattle, WA, November 2012.

Moorman PG. The African American Cancer Epidemiology Study (AACES). Ovarian Cancer in Women of African Ancestry Emerging Consortium Meeting. Bethesda, MD, April 2013.

Moorman PG. Ovarian Cancer: What You Need to Know. Duke Cancer Institute, Cancer Awareness Workshop. Durham, NC, May, August and October 2014.

Moorman PG. Ovarian Cancer in African American Women: The Challenges of Studying a Less Common

Cancer in a Minority Population. Duke Cancer Institute Cancer Control and Population Sciences Seminar Series. Durham, NC, July 2014.

CONSULTANT APPOINTMENTS

National Institutes of Health, Center for Scientific Review

- Epidemiology and Disease Control Subcommittee 2 (EDC-2): Oct. 2000, Feb. 2001
- Special Emphasis Panels: Nov. 2001, Mar. 2002, Nov. 2002, Nov. 2003, July 2004, Nov. 2004, June 2005, Mar. 2006, Nov. 2006, Mar. 2007, July 2007, Nov. 2008, June 2009, July 2009, July 2010, Oct. 2010, Sept. 2011, Dec. 2013, Mar. 2017, Nov. 2017
- Small Grants Program for Cancer Epidemiology: Nov. 2001, Mar. 2003, June 2016, Mar. 2017, June 2017, June 2018, Nov. 2018
- National Cancer Institute, Program Project Review: Jan. 2003, Aug. 2003, Dec. 2003.
- SPORE (Specialized Program of Research Excellence) Review: Breast Cancer Feb. 2005, Ovarian Cancer June 2008, Feb. 2009.

Centers for Disease Control and Prevention. Defining the Public Health Research Agenda for Ovarian Cancer. Invited panel participant. Nov. 2008.

Susan G. Komen for the Cure, Study Section Chair for Post-Doctoral Fellowship in Risk and Prevention, 2010.

Susan G. Komen Breast Cancer Foundation, Study Section Chair for Risk, Prevention and Epidemiology, Member of Programmatic Review Committee, 2005 – 2007.

Susan G. Komen for the Cure/Susan G. Komen Breast Cancer Foundation, Scientific Reviewer, 2003 - 2011.

Department of Defense Breast Cancer Research Program Scientific Peer Review, 1998, 2005, 2007, 2008, 2009, 2013.

Department of Defense Breast Cancer Research Program, Study Section Chair for Training - Epidemiology and Prevention, 2013.

Department of Defense Ovarian Cancer Research Program Scientific Peer Review, 2015, 2016.

Department of Defense Ovarian Cancer Research Program, Study Section Chair for Investigator Initiated Research II, 2018.

National Cancer Institute, Center for Global Health, Data Monitoring Committee for United States – Latin American Cancer Research Network, 2013

CODA, Inc., Research Triangle Park, NC. IRB member, 2004.

National Institute of Environmental Health Sciences Special Emphasis Panel, Technical Evaluation of Support Services for Epidemiology, NIEHS Epidemiology Branch. May 1998.

PROFESSIONAL AWARDS AND SPECIAL RECOGNITIONS

Honorary Physician Assistant, Duke University Medical Center Physician Assistant Program - 2018

Certificate of Appreciation, Duke University Medical Center Physician Assistant Program – 2008

Delta Omega, Public Health Honorary – 1994

The Endocrinologist, Editorial Prize for Volume II – 1993

Research Service Award, National Cancer Institute - 1988-91

Edward E. Smissman Award for Medicinal Chemistry, University of Kansas – 1980

Walter F. Enz Award for Pharmaceutical Chemistry, University of Kansas – 1980

Watkins-Berger Scholarship, University of Kansas - 1975-1980

State of Kansas Scholarship, University of Kansas - 1976-1980

ORGANIZATIONS AND PARTICIPATION

University of North Carolina School of Public Health Alumni Association, Epidemiology Section President, 2001-2002.

Society for Epidemiologic Research

American Pharmaceutical Association

TEACHING RESPONSIBILITIES

Courses Taught

Evidence Based Medicine-I, Duke University, Department of Community and Family Medicine, Physician Assistant program. Primary instructor, 2004-2017.

Evidence Based Medicine-II, Duke University, Department of Community and Family Medicine, Physician Assistant program. Co-Instructor, 2003-2018.

Evidence Based Medicine-I, Duke University, Department of Community and Family Medicine, Physician Assistant program. Lecturer and seminar instructor, 2003.

Epidemiology and Research Methods (PAP 255), Duke University, Department of Community and Family Medicine, Physician Assistant program. Seminar instructor, 2001-2002.

Epidemiology of Cancer (CDE 532B), Yale University, Department of Epidemiology and Public Health. Course director, 1997-2000.

Co-developer of departmental Master's Comprehensive Examination, University of North Carolina-Chapel Hill, Department of Epidemiology, 1995-1996.

Cancer Epidemiology (EPID 233), University of North Carolina-Chapel Hill, Department of Epidemiology, Teaching Assistant, 1992-1993.

Principles of Epidemiology (EPID 160), University of North Carolina-Chapel Hill, Department of Epidemiology, Teaching Assistant, 1990.

Student Mentoring

Helena Furberg, MSPH, University of North Carolina, 1996, Committee Member

Pamela M. Marcus, PhD, University of North Carolina, 1997, Committee Member

Stella Chang, MPH, Yale University, 1997, Committee Member

Mary Riciutti, MPH, Yale University, 1999, Committee Chair

Edward A. Lew, MPH, Yale University, 1999, Committee Member

Shelley Goodstine, MPH, Yale University, 1999, Committee Member

Rupal Desai, MPH, Yale University, 1999, Committee Member

Pei-Yu Lin, MPH, Yale University, 2000, Committee Chair

Lisa Calvocoressi, Ph.D., Yale University, 2003, Dissertation Reader

Rebecca Cleveland, Ph.D., University of North Carolina, 2003, Committee Member

Leah Sansbury, Ph.D., University of North Carolina, 2004, Committee Member

Sumitra Shantakumar White, Ph.D., University of North Carolina, 2006, Committee Member

Katrina Trivers, Ph.D., University of North Carolina, 2006, Committee Member

Amy Dailey, Ph.D., Yale University, 2006, Dissertation Reader

Enid Rivera, M.D., Duke University, 2008, 3rd year Medical Student Preceptor

Alexis Gaines, Duke University, 2013, Master's Committee Member

Chioma Erondu, Duke University, 2013-14, 3rd year Medical Student Preceptor

Tolulope Teniola, Duke University 2016-17, 3rd year Medical Student Preceptor

Tengteng Wang, University of North Carolina, 2018, Committee Member

COMMITTEES AND SERVICE

Standing Committee on Misconduct in Research, Duke University School of Medicine, 2017-present

Senior Faculty Advisory Committee, Office for Research Mentoring, Duke University School of Medicine, 2016-present

Academy of Mentors, Office of Faculty Mentoring, Duke University School of Medicine, 2014-16

Society for Epidemiologic Research. Reviewer for Tyroler and Lilienfeld Prize Papers, 2015

Appointments, Promotions and Tenure Committee, Department of Community and Family Medicine, Duke University Medical Center. Committee Member, 2008-2018

Quality Assurance Sub-Committee for Clinical Research Units, Duke University Medical Center, Committee Chair, 2013-2014

Quality Assurance Sub-Committee for Clinical Research Units (formerly Site-based Research Units), Duke University Medical Center, Committee Member, 2011-2013

Path to Independence Faculty Mentoring Program, Duke University School of Medicine, Peer Reviewer, 2012-2018

Society for Epidemiologic Research. Abstract reviewer for annual meeting, 2011

Cancer Prevention, Detection and Control Research Program, Duke University Medical Center, Cancer Control Pilot Study application reviewer, 2010, 2011

Executive Council, Department of Community and Family Medicine, Duke University Medical Center 2009-present

Education Committee, Department of Community and Family Medicine, Duke University Medical Center, 2009-2017

Faculty Search Committee, Cancer Prevention, Detection and Control Research Program, 2010

Duke Cancer Institute, Editorial Advisory Committee Member, 2010-2011

Duke Comprehensive Cancer Center Annual Meeting, Judge for poster presentations, 2009

Director Search Committee, Cancer Prevention, Detection and Control Research Program, 2009

Partners Allied in Research (PAIR) Pilot Grant application reviewer, Cancer Prevention, Detection and Control Research Program, 2005

Editorial Reviewer

American Journal of Epidemiology
Archives of Gynecology and Obstetrics
Breast Diseases
Cancer
Cancer Causes and Control
Cancer Research
Epidemiology
Gynecologic Oncology
International Journal of Epidemiology
Journal of Community Development
J of the Women's American Medical Assn
Lancet
Nutrition and Cancer
Public Health Nutrition
Women and Health
Annals of Epidemiology
Breast Cancer Research and Treatment
British Medical Journal-Cancer
Cancer Biomarkers
Cancer Epidemiology Biomarkers and Prevention
Clinical Breast Cancer
Ethnicity and Disease
International Journal of Cancer
JAMA
Journal of the National Cancer Institute
Journal of Women's Health
Lancet Oncology
Pharmacogenomics
Trends in Molecular Medicine

CURRENT RESEARCH

Epidemiology of breast and ovarian cancer

Ovarian function after hysterectomy

Racial differences in disease risk and outcomes

Medication use and cancer risk

Etiologic factors for uterine fibroids

EXTERNAL SUPPORT - PAST

Principal Investigator	% effort	Title of Project and Funding Source	Total Costs	Duration
Barbara Hulka	25%	High-Density Lipoprotein Cholesterol and Breast Cancer, National Cancer Institute, R03, Supported dissertation research	$72,234	1992 – 1993

Beth Newman	100%	Carolina Breast Cancer Study, Project 2 SPORE in Breast Cancer, National Cancer Institute, P50.	$1,275,000	1992 – 1995
Beth Newman	50%	Carolina Breast Cancer Study, Project 2 SPORE in Breast Cancer, National Cancer Institute, P50.	$2,511,146	1995 - 1996
Patricia Moorman	50%	Medication Use and Breast Cancer in a Bi-racial Population, National Cancer Institute, R29-FIRST Award.	$498,302	1996 – 2002
Patricia Moorman	0%	Carolina Breast Cancer Study Participant Symposium, North Carolina Division of American Cancer Society Small Grant.	$2500	1997
Patricia Moorman	0%	Carolina Breast Cancer Study Participant Symposium, Susan G. Komen Breast Cancer Foundation Small Grant.	$5000	1997
Joellen Schildkraut	10%	Carolina Georgia Center, Cancer Genetics Network, National Cancer Institute, U-24.	$4,028,129	2002 – 2004
Patricia Moorman	0%	Non-steroidal Anti-Inflammatory Drugs and Breast Cancer: A Study of Gene-Environment Interactions among African-American and White Women, Minority Serving Institution Partnership Grant, Pilot Funds.	$28,040	2003 – 2004
Celette Skinner	5%	Partnerships to Eliminate Disparities in Cancer Outcomes and Research, National Cancer Institute, National Cancer Institute.	$517,743	2002 – 2006
Patricia Moorman	0%	Diversity Supplement to RO1 AG020162 Ovarian Failure Among Hysterectomized Women, National Institute on Aging (Note: Grant was awarded but post-doc accepted another position.)	$169,720	2006
Andrew Berchuck	5%	Biological Basis for Chemoprevention of Ovarian Cancer, Department of Defense.	$824,000	2002 – 2007
Stephen Freedland	5%	Weight Loss and Gain and Cancer Free Survival after Radical Prostatectomy in a Multiethnic Cohort. Prostate Cancer Foundation.	$100,000	2007-2009
Joellen Schildkraut	10%	Genetic Modifiers of BRCA1 and BRCA2, Project 3 SPORE in Breast Cancer. National Cancer Institute.	$1,795,862	2003 – 2009
Joellen Schildkraut	10%	Molecular Epidemiology of Ovarian Cancer. National Cancer Institute.	$3,750,000	2003 – 2010

Patricia Moorman	40%	Ovarian Failure among Hysterectomized Women. National Institute on Aging.	$3,781,480	2003 - 2010
Patricia Moorman (Sub-contract PI)	3%	Cancer Genetics Network. National Cancer Institute.	~$25,000	2010 – 2012
Laura Havrilesky	15%	Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer. Agency for Healthcare Research and Quality	$486,476	2010 - 2012
Jeffrey Marks	5%	Atlantic Breast and Gynecologic Clinical Validation Center. National Cancer Institute	>$1,500,000	2010 - 2013
Cathrine Hoyo	5%	Disparities in Cervical Cancer Precursors and Deregulation of Imprinted Genes National Cancer Institute	~$200,000	2012 – 2013
Emanuel Trabuco (Moorman, Duke PI)	2%	Anti-Müllerian Hormone as a Marker of Ovarian Reserve in Women with and without Hysterectomy. Mayo Clinic Internal Funds	$100,000	2012 – 2013
Evan Myers	10%	Systematic Review of Cancer Screening Literature for Updating American Cancer Society Breast Cancer Screening Guidelines American Cancer Society	~$400,000	2013 - 2014
Joellen Schildkraut	9%	Cancer Education and Career Development Training Grant. National Cancer Institute	~$1,400,000	2009 – 2014
Patricia Moorman (Sub-contract PI)	5%	Rare Cancer Genetics Network National Cancer Institute	~$240,000	2010 – 2016
Joellen Schildkraut (Moorman, co-PI)	20%	Epidemiology of Ovarian Cancer in African American Women National Cancer Institute	~$12,000,000	2010 – 2017
Gillian Sanders	10%	Management of Infertility Evidence-Based Practice Center		2015-2016
Gillian Sanders	10%	Management of Labor Dystocia Evidence-Based Practice Center		2016
Gillian Sanders	15%	Office of Women's Health – Topic Development Evidence-Based Practice Center		2016
Evan Myers	5%	Comparing Management Options for Management: Patient-centered Results for Uterine Fibroids (COMPARE-UF) PCORI	~$19,000,000	2014 – 2018

EXTERNAL SUPPORT - CURRENT

Principal Investigator	% effort	Title of Project and Funding Source	Total Costs	Duration
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PERSONAL INFORMATION

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Exhibit 22

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

RULE 26 EXPERT REPORT OF ANNE MCTIERNAN, MD, PHD

Date: November 16, 2018

Anne McTiernan
Anne McTiernan, MD, PhD

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Mandate

I have been retained to review the current state of the scientific literature regarding talcum powder products and opine on whether those products cause ovarian cancer. When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products and all constituent elements contained within. All my opinions in this report are based upon a reasonable degree of scientific and medical certainty. My time is billed at $450 per hour for the literature review and preparation of this report. I have not previously provided expert testimony in legal cases.

Credentials, Expertise, and Experience

I am a Full Member at the Fred Hutchinson Cancer Research Center in Seattle, Washington, Division of Public Health Sciences, Program in Epidemiology. I am also a Full Research Professor at the University of Washington School of Public Health, Department of Epidemiology, and the University of Washington School of Medicine, Department of Medicine, Division of Geriatrics. I am an elected member of the American College of Epidemiology, the Obesity Society, and the American College of Sports Medicine. From 2002-2012, I directed the Fred Hutchinson Cancer Research Center's Prevention Center.

I have received several prestigious awards for my research work including: the American College of Sports Medicine Wolffe Lecture, 2018, the American College of Sports Medicine Citation Award, 2012; the McDougall Mentoring Award, Fred Hutchinson Cancer Research Center, 2011; Komen for the Cure Scientific Advisory Council/Komen Scholars, 2010-2012; the University of Washington Roger E. Moe Award for Translational Research 2009; and the Joan P. Liman MD Award, Recipient, New York Medical College, 1989.

I received my PhD in Epidemiology in 1982 from the University of Washington, and my MD degree in 1989 from New York Medical College. I completed Internal Medicine residency training from the University of Washington in 1992. For the past 25 years, I have focused on epidemiologic research, primarily in cancer and women's health. My research studies used the methodology employed in the talcum powder products and ovarian cancer studies, namely, case-control studies, cohort studies, and meta-analyses. In addition, I have had leadership positions for several randomized controlled trials

testing interventions to prevent cancer. I have published over 400 scientific manuscripts in peer-reviewed medical and scientific journals, have contributed to several academic texts, and have edited two academic texts.

I have held several leadership positions in scientific U.S. Government work. Most recently, I was a member of the 2018 U.S. Department of Health and Human Services Physical Activity Guidelines Advisory Committee and was a member of the 2008 U.S. Department of Health and Human Services Physical Activity Guidelines Advisory Committee. I served as chair of the Cancer subcommittees for both Committees. I have served on, or chaired, grant review panels for the U.S. Department of Defense Congressionally Directed Medical Research Programs and the National Institutes of Health, and serve as a program reviewer for NCI intramural epidemiologic research branches and for NCI comprehensive cancer centers.

I have served on editorial boards for the American Association for Cancer Research Cancer Prevention Journal, the Journal of Women's Health, and Medscape Women's Health. I have reviewed manuscripts for over a dozen prestigious journals including: JAMA, Journal of the National Cancer Society, Archives of Internal Medicine, American Journal of Epidemiology, Annals of Internal Medicine, European Journal of Cancer, British Journal of Cancer, Cancer Causes & Control, Cancer Epidemiology Biomarkers & Prevention, Annals of Epidemiology, Epidemiology, and Nutrition.

My research funding has been provided by the U.S. National Cancer Institute, the National Institutes of Health, the National Heart Lung & Blood Institute, Komen for the Cure, the Breast Cancer Research Foundation, National Cancer Institute Canada, and various pharmaceutical companies and other foundations. I have been Principal Investigator of several randomized clinical trials testing effects of various agents in relation to prevention of breast and other cancers, including exemestane, raloxifene, tamoxifen, aspirin, and vitamin D. In addition, I have been Principal Investigator of four randomized clinical trials testing effects of weight loss and exercise on biomarkers of breast and other cancers. I am co-investigator of a pending National Cancer Institute funded trial testing the effect of exercise on quality of life in women with ovarian cancer. I was Principal Investigator of the Seattle site of a prospective cohort study of 1100 breast cancer survivors that investigated associations of hormones, inflammation, diet, exercise, obesity, and breast cancer survival. I was Principal Investigator of a case-control study of thyroid cancer and hormones in women, and co-investigator of a case-control study of

breast cancer in men. I have published on data from other case-control studies including studies on breast cancer, pituitary tumors, melanoma, and colorectal adenomas. I have collaborated in several prospective cohort studies, resulting in lead, senior, and co-authorship of several epidemiologic manuscripts. These included the Women's Health Initiative Observational Study, the Tromso study, the Carotene and Retinol Efficacy Trial cohort, the VITAL cohort, and the Pancreatic Cancer Cohort Consortium.

While my major focus is in epidemiology of breast cancer, I have also published on ovarian cancer, on gynecologic cancers in general, and on women's cancers, as described below, as well as on colorectal, pancreas, melanoma, and prostate cancers. In my randomized clinical trials and prospective cohort studies, I have investigated the effects of weight loss and exercise on biomarkers of inflammation, which is highly relevant to the topic of this report, because inflammation may be one mechanism linking talcum powder products exposure and risk of ovarian cancer.

My international work in epidemiology has included work with the International Association for Research in Cancer (IARC), the World Cancer Research Fund, and the Norwegian Tromso and EBBA studies. For IARC, I chaired a working group on mechanisms for a monograph on obesity, physical activity, and cancer risk (IARC Handbook of Cancer Prevention 2002: Physical Activity and Weight Control, 2000-1). For the World Cancer Research Fund, I am a member of the advisory panel of experts that guides interpretation of meta-analyses and systematic reviews of nutrition, physical activity, obesity, and risk for many cancers including ovarian cancer (http://wcrf.org/sites/default/files/Ovarian-Cancer-2014-Report.pdf).

From 1992 to 1997, I was the Project Director for clinical work at the Women's Health Initiative Clinical Coordinating Center. I held this role from the inception of the Women's Health Initiative, and therefore directed all aspects of development and implementation of the three clinical trials and observational study. This included development of questionnaires and protocols. Of interest to ovarian cancer and talcum powder products, one of the Women's Health Initiative questionnaires includes questions about use of talcum powder products. Furthermore, ovarian cancer was one of the primary cancers included as an outcome in this study. As Project Director, I oversaw development of the protocol and procedures for ascertainment and adjudication of cancer outcomes, including ovarian cancer. When I stepped down as Project Director (to lead my own National Cancer Institute funded studies), I retained leadership of

the outcomes work for the Women's Health Initiative through 2005. This outcomes work entailed identifying cases of specific diseases such as cancer (including ovarian), collecting medical records, and classifying cases according to standardized criteria.

Although I have not personally conducted research on talcum powder products use and risk for ovarian cancer, I have published several manuscripts on gynecologic cancers, including prevention of ovarian cancer in women at high genetic risk, as well as effects of weight and exercise on risk for ovarian cancer and on survivorship in ovarian cancer patients. In addition, I am co-investigator of a National Cancer Institute grant to test an exercise intervention on quality of life in women with ovarian cancer.

While my expertise is in the area of epidemiology, primarily in women's health and cancer research, I regularly consider the reports and studies from different scientific and medical fields including pathology, oncology, gynecology, physiology, molecular biology, and toxicology, and therefore, I have experience and expertise to consider evidence presented by experts in these fields, as I do when I prepare scientific manuscripts and grant proposals, when I review grants and manuscripts for government and private funding agencies, and when I do peer-reviewing for scientific and medical journals. Attached as Exhibit A to this report is a current copy of my curriculum vitae.

Overall Approach

The foundation for this report is based upon my education, expertise, and years of experience in designing, conducting, and interpreting epidemiologic studies, as well as my medical training. I drew upon my years of experience with synthesizing and interpreting large numbers of epidemiologic studies for comprehensive reports including work for the U.S. government, the World Health Organization International Agency for Research on Cancer (IARC), and the World Cancer Research Fund. My opinions are based on the published epidemiologic evidence including original case-control and cohort studies, systematic reviews, meta-analyses, and pooled analyses on the topic of talcum powder products exposure and risk of ovarian cancer. In reviewing the epidemiologic literature, I used my experience as a researcher in evaluating study quality, and in determining evidence of association between talcum powder products and ovarian cancer in terms of estimated size of the effect and statistical significance. I drew upon my 36 years as a PhD-trained epidemiologist and 26 years as an MD-trained clinical scientist.

In developing my opinions in this report, I applied the same rigor and standards as I utilize in my academic and research work. In addition to my review of epidemiologic studies, I also considered and reviewed clinical, pathological, and biologic and mechanistic evidence regarding talcum powder product exposure and ovarian cancer development.

Executive Summary

This review assessed relevant published epidemiologic evidence on the association between use of talcum powder products in the genital/perineal area and risk of developing epithelial ovarian cancer. My review, as discussed more fully in this report, included 38 publications in Medline referenced scientific journals. Of these papers, 28 presented data from case-control studies(1-28), 5 presented results from 3 cohort studies(29-33), 7 were meta-analyses of all epidemiologic studies up to a set date(11, 22, 34-38), and 1 was a pooled analysis of 8 case-control studies(39). All of these form the basis for the conclusions below. The meta-analyses, which included data summarized from all published case-control and cohort studies, consistently showed that ever use of talcum powder products in the genital/perineal area is associated with a statistically significant 22 - 31% increased risk of developing epithelial ovarian cancer overall compared with never-users. Further, the meta-analyses found a statistically significant 24 – 32% increased risk of developing serous ovarian cancer—the most common subtype of epithelial ovarian cancer—in women who had ever used talcum powder products compared with never-users. The pooled analysis, which included data from 5 previously published and 3 unpublished case-control studies, found similar statistically significant increased risks for overall epithelial ovarian cancer and serous ovarian cancer (24%). The two most recent meta-analyses, and the pooled analysis, found evidence of relationships between increasing amount of exposure to talcum powder products in the perineal/genital area (including frequency, years of use, and estimates of lifetime applications) and increased risk of developing epithelial ovarian cancer (i.e., dose-response relationships).

Published laboratory and clinical studies on talc exposure and ovarian carcinogenesis have shown that in humans, talc can migrate from the perineum to the ovaries and that it can cause an inflammatory response. Elevated levels of biomarkers of inflammation (such as cytokines), as well as oxidative stress, provide biologically plausible pathways by which talcum powder product exposure can induce neoplastic transformation and result in ovarian cancer.

Given the frequency with which asbestos, a known carcinogen has been found in cosmetic and personal-use talc products, I reviewed the literature on the epidemiology of asbestos and risk of ovarian cancer. Due to the presence of not only asbestos but fibrous talc, heavy metals, and fragrance, I also reviewed literature on the carcinogenic properties of these constituents. IARC noted in its 2012 report that a causal association between exposure to asbestos and cancer of the ovary was clearly established.(40,

41) IARC has classified asbestos and talc containing asbestiform fibers grown in an asbestiform habit as Class 1 carcinogens(40, 42). Talc fibers grown in an asbestiform habit are often referred to as "fibrous talc." The elongated features of fibrous talc have many of the carcinogenic properties of asbestos that are known to cause an inflammatory process.(40) The additional chemicals present in talcum powder products discussed above were also classified by IARC to be carcinogenic(40), contributing to the biologically plausible mechanisms to explain the carcinogenic effects of talcum powder products.

The epidemiologic evidence in total, along with the biological and pathological evidence, fits virtually all of the Bradford Hill aspects of causation(43), namely: strength, consistency across populations, temporality, biologic gradient (dose-response), plausibility, coherence, and analogy. The weight of the evidence related to genital use of talcum powder products and ovarian cancer development demonstrates a consistent increased risk. There are many instances in which relative risks less than 1.5 are widely accepted within the scientific community as being causative and have strong public health and clinical ramifications, as I point out in the report. Given the high prevalence of use of talcum powder products (as much as half of women in some studies), a relative risk/odds ratio in the range observed in these studies can have profound effects on clinical events and public health.

In my opinion, as an epidemiologist and physician, stated to a reasonable degree of medical and scientific certainty, use of talcum powder products, including Johnson & Johnson Baby Powder and Shower to Shower, in the genital/perineal area can cause ovarian cancer. I base this opinion on the statistically significant elevated risk estimates (relative risk, odds ratios) seen when the epidemiologic data are combined, the pathological evidence, the consistency of results across geographic areas and in different race/ethnic groups, the evidence of a positive dose-response effect, and the plausible biological mechanisms.

The Science of Epidemiology

Epidemiology is the science of diseases in human populations. Epidemiologists study patterns of disease occurrence to determine causes of the disease of interest, with an aim of finding ways to prevent the disease from occurring. Epidemiological research describes and seeks to explain the distribution of health and disease within human populations. Its methods are based mainly on comparative observations made at the level of individuals within populations. This type of investigation is known as observational. By relating differences in circumstances and behavior to differences in the incidence of disease, associations are identified that may or may not be causal.

In epidemiological studies, an 'exposure' is a factor or condition that may or may not influence the risk of disease. For assessing effects of some exposures, epidemiologists may employ randomized controlled clinical trials, but for exposures that have possible adverse effects with little known benefit, such studies would be unethical. For example, the effects of vitamin supplements have been tested in large-scale clinical trials to determine effects on risk for several cancers. This was considered ethical because the expectation was that the vitamin supplements could have benefit, and were unlikely to have risk, for study participants. For toxicological exposures, however, with little expectation of benefit to offset possible adverse effects, observational studies will usually be the only available epidemiological evidence.

Much public health knowledge derives from epidemiological studies. For example, observational epidemiological studies show us that individuals who drink excessive amounts of alcohol have a high risk for developing liver failure and other diseases. Such studies have shown that persons with obesity have a high risk for developing diabetes and that smokers have high risk for developing lung cancer. Similarly, the effects of toxic agents on risk for several diseases have been identified through observational epidemiological studies. Examples include the effect of lead paint on cognitive development in children; the effect of radium exposure on bone health, blood abnormalities, and cancers; and the effect of second hand smoke on risk for lung cancer in nonsmokers.

The associations between talcum powder product use and risk for ovarian cancer have been studied only in two types of epidemiologic studies—case-control and cohort—and therefore this description of epidemiologic methodology below is limited to those types of studies.

Terminology in Epidemiological Studies

Disease incidence: The incidence of a disease is the number of new cases that occur. An incidence rate is the number of new cases that occur per number of persons over an interval of time. Typically, for cancer, incidence rates per 100,000 individuals per year are determined. The incidence rate for ovarian cancer in the U.S. is approximately 11.7/100,000 women/year (https://seer.cancer.gov/statfacts/html/ovary.html).

Risk: The risk of a disease refers to likelihood of its occurrence. In epidemiological studies, risk is usually used in relative terms, that is, the risk of developing cancer in one group versus the risk in another group. In cancer epidemiology, the risk almost exclusively refers to risk of incident cancer, that is, risk of a new cancer occurrence.

Risk factor: The World Health Organization defines a risk factor as any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury (http://www.who.int/topics/risk_factors/en/). Risk factors can be inherent, such as sex, age, and genetics; lifestyle-related such as diet, physical activity, or smoking; health related such as menstrual factors, reproductive history, or history of infectious diseases; toxic exposures such as minerals, metals, chemicals, or radiation; or medical, such as use of particular medications.

Exposures: In epidemiological studies, an ‘exposure’ is a factor or condition that may increase or decrease the risk of disease. In this report, use of talcum powder products is the ‘exposure’ investigated. Self-reporting of exposure could result in incomplete information. Some women may over-report use of personal products, while others may not recall whether they used the products, how often or at what quantity they used them, or for how long they continued using them. Studies in which participants are queried by trained interviewers may be able to obtain information in greater detail than when participants complete questions on a form.(44) However, women may be reluctant to relay sensitive personal information to an interviewer as opposed to a self-administered form.(44) This type of

systematic bias, however, would underestimate the relative risk, suggesting that effects of talcum powder product use in the perineal area may be stronger than reported in epidemiologic studies.

Association: Epidemiologists use the term association to describe how a disease occurrence varies as a result of the effect of an exposure. A positive association indicates that the exposure increases risk of the outcome; a negative association indicates that the exposure decreases risk of the outcome.

Etiology: The etiology is the cause or origin of a disease or condition.

Multi-factorial etiology: Very few cancers occur as a result of only one cause. Most, on the other hand, have several likely causes, each with different levels of effect. The most common risk factor for cancer is age, as older persons have increased risk for developing most of the common cancers. So, even though certain human papilloma viruses increase risk for head and neck cancers, their effect is most often seen with increasing age despite individuals acquiring the virus at a young age. For some cancers, exposures add to the effects of other exposures, or even multiply their effects. For example, both smoking and alcohol use increase risk for squamous cell carcinoma of the esophagus, but individuals who both smoke and drink have a risk of this cancer that is greater than what would be expected by adding the effects of the two exposures.

Latency period: The length of time between when a person is exposed to a causal agent and when their cancer is first diagnosed is called the latent period. This period is typically years to decades. For exposures that continue over time, it may not be possible to determine the latency period of that cancer.

Relative risk, odds ratio, and hazard ratio: The strength of a relationship between an exposure and the occurrence of disease is commonly expressed in terms of relative risk. In cohort studies, relative risk is the ratio of risk (or incidence) of a disease among people with an exposure to that among people without that exposure. In cohort studies, the hazard ratio can be used, and is the chance of an event occurring in one group (exposed) divided by the chance of the event occurring in another group (non-exposed). In case-control studies, the odds ratio is used, which is the ratio of the odds of exposure among cases to the odds of exposure among controls. Relative risks, odds ratios, and hazard ratios

above 1.0 indicate an increased risk, while those below 1.0 imply a protective effect. Therefore, a relative risk of 1.3 represents a 30% increased risk.

Statistical analyses: Epidemiologists use several types of statistical analyses to determine the size and significance of relationships among variables in sets of data. The most common in observational studies are the relative risk, odds ratio, and hazard ratio. These estimates are based on individual studies, or on meta-analyses, which are based on data from multiple studies. To determine the likelihood of these being true estimates of risk, rather than just occurring by chance, epidemiologists determine the statistical significance. For the relative risk, odds ratio, and hazard ratio, we calculate a confidence interval (CI), which shows the range of values that the true risk estimate likely represents. Most commonly, we use 95% CI, which means we are 95% sure that a true relative risk or odds ratio lies within that interval of numbers. If a confidence interval includes the number 1.0, then we say the association between the exposure and the disease could be null. Some epidemiologists consider a CI that has 1.0 at one end of the range to be of "marginal statistical significance." A similar statistic is the p-value, which estimates how likely the observed association is likely due to chance. Epidemiologists often consider a p-value less than or equal to 0.05 as "statistically significant," and often describe p-values between 0.05 and 0.09 as "marginally statistically significant." However, the term just refers to the likelihood of a chance finding.

Both confidence intervals and p-values depend largely on the size of the population studied. If a relative risk/odds ratio indicates an effect that is consistent across studies, or that is large, we are less likely to reject the likelihood of true association, even if the confidence interval includes 1.0 or if the p-value is greater than 0.05.

Sample size: Because development of cancer can be a random event, epidemiologists strive to determine whether an association between an exposure and disease could have occurred by chance. If the study is designed appropriately, the chance of random-ness explaining observed associations is lessened. The number of cases of cancer within the study is a critical element to determining likelihood of causality.

Standardized incidence ratio and standardized mortality ratio: In some epidemiologic studies, only highly exposed persons are available for study. This is a common occurrence in studies of occupations with high levels of exposures to carcinogens, such as asbestos. Researchers typically then compare the incidence (or mortality) in the exposed cohort with the general population from which the exposed cohort is drawn. The standardized incidence ratio compares the actual versus expected number of cases of a disease, using the population data to determine expected numbers. Similarly, the standardized mortality ratio compares actual versus expected numbers of cause-specific or overall deaths. The standardized incidence ratio and standardized mortality ratio are similar to relative risks, and 95% confidence intervals are often presented.

Dose-response: “Dose response” began as a medical concept where it denotes a change in the effect of a medication or treatment according to the dose used. This concept can be applied to any exposure, including potentially toxic agents such as talcum powder products. The demonstration of a biological gradient adds weight to evidence that an exposure may be causal.

Dose response effects may be linear, where an increase in the exposure increases risk of disease at each level of increase in the exposure. A common example is the relationship between average packs/day and years of cigarette smoking and risk for lung cancer. Alternatively, there may be a ‘threshold’ below which there is no effect seen, but above which there is an effect. An example is the association between exposure to menopausal hormone therapy; use for short periods has little effect on risk of breast cancer, but risk consistently increases for five years’ or longer use.

Alternatively, the effect may be to influence risk one way at both low and high levels of exposure, but the other way at intermediate levels of exposure, shown as ‘J’- or ‘U’-shaped curves. In such cases, the exposure is evidently beneficial or harmful only within certain ranges. For example, intake of alcohol at small amounts has been related in some studies to lower risk of cardiovascular disease, whereas heavy intake increases risk.

Some exposures that are continuous variables are often reported in discrete categories. Although this is done for statistical reasons and can make effects easier to detect, the number and location of category boundaries may obscure the true relationship between exposure and the outcome, and non-linear effects of exposure may be missed if inappropriate categories are used.

Bias: A systematic error in the design, recruitment, data collection or analysis that results in a mistaken estimation of the true effect of the exposure and the outcome.

Confounding: This type of bias occurs when a third variable interferes with a true relationship between an exposure and an outcome. A confounding variable is one that is related to the risk of disease and to the exposure. It is not by itself a cause of the disease and does not lie in the pathway between the exposure and disease. A classic example is that individuals who report carrying matches in their pockets are more likely to develop lung cancer than individuals who do not carry matches. However, the true relationship is between smoking and lung cancer. Smokers are more likely to carry matches, and it is the smoking that is the true cause. The epidemiologic studies reviewed for this report all adjusted for potential confounding factors.

Effect modification: In some persons, an exposure increases risk of disease while in others it has no effect or has a smaller effect. This is called effect modification. An example is that obesity has a larger effect on risk for colon cancer in men than in women.

Generalizability: The goal for epidemiologic research is to identify causes of disease that can be applicable to all populations. Most modern-day case-control studies attempt to do this by conducting population-based studies. That is, they identify all cases of a cancer occurring in a population and attempt to interview as many of those cases as possible. They also identify a similar sample of persons from the same population who do not have cancer and attempt to interview as many of those as possible. Many of the case-control studies of talcum powder products identified cases through population-based cancer registries, which register almost 100% of cases of cancer occurring in the population served by the registry. These population-based studies are better able to produce results that are generalizable to the whole population. Hospital-based case-control studies of ovarian cancer include all cases of the cancer that present to a hospital and compare them to a comparable group of hospitalized patients without cancer. While the comparisons between cases and controls can be valid, the generalizability of the results to the population can be low if patients from the recruiting hospital differ from the population as a whole.

Generalizability can be more of an issue for cohort studies, depending on how the study participants were recruited. Three cohort studies have reported on talcum powder product use and ovarian cancer risk. The Women's Health Initiative recruited from the general population of postmenopausal women from 40 clinical centers around the U.S. The rate of response was only around 1-2%, however, and therefore the cohort is unlikely to represent the population of American postmenopausal women. The Nurses' Health Study recruited nurses from around the U.S. Their rate of response was higher than for the Women's Health Initiative, but they are all nurses, and therefore have different health knowledge, income, and socioeconomic status compared with the general U.S. population. The Sisters' Study recruited from the general population, targeting women who had at least one sister with breast cancer. The responding participants therefore represent only women with a family history of breast cancer, and given their self-selection, likely differ from the general population in vulnerability to cancer and other characteristics.

Exposure measurement: Defining whether a person is exposed to a potentially causal agent is critical to the science of epidemiology. For many exposures, we must rely on what the individual can tell us about their health habits, lifestyle, work history, and use of products and medications. Recall of these variables can be challenging. Epidemiologists, therefore, often have interviewers use tools to jog participants' memories, such as anchoring around particular ages and life events. The most thorough case-control studies queried about both frequency and duration of use of talcum powder products, as well as brand and type of product, and areas of exposure (e.g., perineal, sanitary napkin, other body areas, diaphragm, etc.) The ascertainment of use of talcum powder products is difficult, especially in determining dose of exposure, because women may have been using powders without being aware of what the product contained. Furthermore, information on the variable contents of talcum powder products (talc, fibrous talc, asbestos, other metals, fragrance) was not available to the scientists conducting the epidemiologic studies. While many epidemiologic case-control studies of talcum powder products and ovarian cancer risk asked women for brand names and dates of use, and analyzed data separately by likely powder contents, these analyses will not have been able to identify the various constituents of talcum powder products.

The Women's Health Initiative asked about duration of use of talcum powder products but did not ask about frequency of use.(29) The Nurses' Health Study asked about frequency of use but did not query regarding duration of use.(31) The Sisters' Study asked participants about use of talcum powder

products in the 12 months before study enrollment, and the frequency of use.(30) None of the cohorts, therefore was able to estimate total lifetime dose of talcum powder product exposure. As described below, under-reporting of exposures will underestimate a true relative risk.(45) Therefore, the estimated relative risks in studies that looked at effects of talcum powder product use and risk of ovarian cancer may be under-estimates.

Diagnosis and classification of disease outcome: "Outcome" refer to the disease or health condition of interest; in this report, any type of epithelial ovarian cancer is the outcome. In some reports, cancers of the fallopian tubes and peritoneum are combined with epithelial ovarian cancer, as they are believed to be the same biological process and are treated the same as ovarian cancer with surgery and chemotherapy (https://www.cancer.gov/types/ovarian/hp/ovarian-epithelial-treatment-pdq).

Determination of outcomes (sometimes called "events") is a critical part of epidemiologic research. If cases of a disease are over- or under-counted, results of exposure-disease associations will be skewed. If the source of cases differs from the source of controls, comparisons between cases and controls may be biased. In case-control studies, researchers try to include all cases that were newly diagnosed with the disease in a defined population within a set period. Population-based cancer studies often identify cases through population-based cancer registries. Hospital-based studies, conversely, identify cases that were newly diagnosed in one or more hospitals. Whichever method is used, researchers try to include and interview as high a proportion as possible of identified cases, to reduce chances of biased results.

For epidemiologic studies of cancer, it is important to identify, at the minimum, the type of cancer, stage of cancer at diagnosis, and subtype of cancer. Using pathologists' reports from medical records, trained coders classify patients into the correct categories depending on the pathology and other medical records. There are several different subtypes of cancer of the ovary. Over 90% originate in epithelial tissues and are called "epithelial ovarian cancers." The remaining 10% originate in other ovarian tissues (germ cell or sex-cord stromal). Of the epithelial ovarian cancers, approximately 70% are serous, 10% are endometrioid, 12% are clear cell, 3% are mucinous, 1% are Malignant Brenner, and the remaining are mixed histologies.(46) Epithelial ovarian cancer may be invasive or borderline. Only epithelial ovarian cancer has been studied in relation to use of talcum powder products. Therefore, in this report, "ovarian cancer" refers to "epithelial ovarian cancer."

Types of Epidemiologic Studies on Ovarian Cancer and Exposure to Talcum Powder Products

Epidemiologists have assessed the relationships between use of talcum powder products and risk of ovarian cancer development, using several types of epidemiologic studies. The studies with the greatest number of cases of ovarian cancer used case-control designs. Most of these were designed specifically to address use of talcum powder products as a potential cause of ovarian cancer. Three cohort studies have also reported on associations between talcum powder product use and risk of ovarian cancer. These cohort studies were designed to test hypotheses relating hundreds of exposures to scores of disease outcomes including common cancers, cardiovascular disease, cerebrovascular disease, musculoskeletal diseases, and others. Finally, after several epidemiologic studies were published, researchers combined data from these studies using either meta-analyses or a pooled analysis. The pooled analysis also included data from previously unpublished studies, and therefore provide additional information beyond just summarizing results of published studies. All of these studies contribute to the science of the epidemiologic evidence relating use of talcum powder products to risk of ovarian cancer development. The totality of evidence on the causal effect of talcum powder product use on ovarian cancer development relies on data from epidemiologic studies, pathological evidence of migration to the ovaries of talc and other contents of talcum powder products (such as asbestos), and laboratory evidence.

Critical Components to Both Case-control and Cohort Studies

1) The accurate and complete ascertainment of cases. In case-control studies, this means that all cases of ovarian cancer should be identified in a given population and as high percent of them should be included in the study as possible. The controls should be free of ovarian cancer and should be as similar as possible to the cases except for the exposure under study. In cohort studies, this means that all individuals should be followed over time to determine how many did or did not develop ovarian cancer. For both types of studies, cases should be confirmed by medical record and pathological report review.

2) Precise determination of exposure. In both case-control and cohort studies, both cases and non-cases should have completed questionnaires about their current and past history of use of talcum powder products, including how often they used the products, when they began use, and number of years used.

In case-control studies, this is often done with the help of a trained interviewer. In cohort studies, which typically involve larger numbers of participants because only a small fraction will go on to develop specific diseases, questionnaires are usually self-administered without the assistance of an interviewer. In cohort studies, exposures should be updated after the baseline assessments, to ensure that changes in exposure can be captured. For an exposure like talcum powder product use, lifetime use would be relevant for determining total exposure. For both case-control and cohort studies, determining early life exposures depend on participants' ability to recall typical use patterns. Interviewer-administered surveys would typically include prompts to help participants recall past habits. Self-administered questionnaires may include some printed prompts, but these are usually minimal.

For a rare endpoint like ovarian cancer, a cohort must be followed for decades in order for a sufficient number of cases to accrue to determine effects of particular exposures. Therefore, there is the possibility of bias towards the null via changes in behavior over the course of the decades of follow-up. A woman who was originally classified as an "ever" talc user will remain an "ever" user even if she subsequently discontinued talc use. A "never" user who subsequently begins talc use will always be misclassified as a never user unless a follow-up survey records her change in status.

In ideal situations, the precise nature of the exposure would be verified. Despite habitual use, however, quantification of exposure is difficult.

(3) For both case-control and cohort studies, the populations should be well-characterized, so that any potential confounding variables can be accounted for in comparing exposure rates of cases and non-cases.

Case-control Studies

In case-control studies, individuals diagnosed with a specific type of cancer (cases) are compared with otherwise similar individuals who have not been diagnosed with cancer (controls). The control group is a sample of the population from which the cases arose and provides an estimate of how the exposures being studied are distributed in that population. In the ideal case, the controls will be similar to the cases on all variables other than the exposure under question. Therefore, epidemiologists often match

controls to cases on such variables as age, race, and ethnicity, or they include a large enough sample of participants that they can adjust for these variables.

Case-control studies can enroll a large number of cases, are usually less expensive than cohort studies, and can be completed over shorter periods of time. Relevant to this report, case-control studies also can be designed to answer specific questions related to one outcome, and participants can be queried in detail about certain exposures. Selection bias is an increasing problem if participation rates among case and control groups is substantially less than 100 percent, and where participation may be related (in different ways) to various exposures.

Case-control studies are subject to their own limitations, including recall bias, which can occur when participants' reports of various exposures are differentially affected by whether they are cases or controls in the study. This is a theoretical bias however; studies that have investigated other sources of data on exposures have failed to confirm the presence of differential recall between cases and controls.(47)

One of the case-control studies of talcum powder product use and ovarian cancer risk (1) addressed this issue by counting as "users" only women who had used talcum powder products for at least six months, on at least a monthly basis. This procedure minimizes the potential over-reporting of minimal exposure by cases versus controls.

For this report, I reviewed 28 case-control studies, for most of which the association between use of talcum powder products and risk of ovarian cancer was a primary research questions.

Cohort Studies

In prospective cohort studies (usually called cohort studies), the exposures of a large group (cohort) of people who are assumed to be healthy are assessed, and the group is followed over a period of time. During the follow-up period, some members of the cohort will be diagnosed with cancer, while others will not, and comparisons are then made between these two groups. Cohort studies may need to be very large (up to hundreds of thousands of participants) to have sufficient statistical power to identify factors that may increase cancer risk by on the order of 20 or 30 percent. In addition, meaningful

comparisons between cases and non-cases can be made only for factors that vary sufficiently within the cohort. Importantly, cohort studies must identify exposures of interest when participants are enrolled into the study, in order to determine effect of the exposures on eventual development of the outcome of interest. Alternatively, if an exposure is ascertained some time after enrollment (as in the Nurses' Health Study ascertainment of talcum powder product use), the researchers will consider the date of collection of that exposure data to be the start date for follow-up of study participants. Because cohort studies typically are designed to look at multiple outcomes such as cancers, cardiovascular diseases, mortality, and other diseases, information collected on exposures tends to be minimal, to pertain to current levels of exposure, and may not be updated during follow-up.

Cohort studies provide the opportunity to obtain repeated assessments of participants' exposures at regular intervals, which may improve the assessment of the exposures. However, for this to happen, the investigators need to have planned for repeated measures of the exposure. In published cohort studies of talcum powder products and ovarian cancer risk, no repeated measures of talcum powder products were reported.

In cohort studies, the ascertainment and adjudication of cancer outcomes can be accomplished by directly asking participants about illnesses and hospitalizations, and requesting medical records for reviewing these events. In some cases, ascertainment of disease events may be accomplished by linking to a cancer registry.

For this report, I reviewed results of 3 cohort studies, published in 5 papers. None were designed specifically to look at the association between talcum powder product use and risk of ovarian cancer. Further, none of these studies fully ascertained exposure to talc, as will be discussed below.

Meta-analyses

Because there can be random variations within individual epidemiologic studies, and because very large sample sizes may be needed to see effects on rare diseases, epidemiologists rarely make causal inferences based on results of one study. Rather, we look at the totality of epidemiologic studies to determine patterns of exposure-disease relationships. Meta-analysis is a method used to combine the statistical results of several studies to produce an average estimate of effect of an exposure on an

outcome of interest. These summary estimates can provide evidence regarding the presence or absence of an association and can allow examination of dose-response relationships. In the area of talcum powder products use and ovarian cancer, 7 meta-analyses have been published (11, 22, 34-38), two of which are very recent and covered all studies contained in the previous meta-analyses.(34, 35) Of the 7 meta-analyses, 2 were included within reports of individual case-control studies (11, 22); the two recent meta-analyses contained all studies included in these 2 meta-analyses as well.

Pooled analysis is a type of meta-analysis where original individual-level data from various published and/or unpublished epidemiological studies are combined and re-analyzed. The combination of data from multiple studies creates a larger data set and increased statistical power. One such pooled analysis was published on the relationship between talcum powder product use and risk of ovarian cancer, and is heavily cited in this report because of its significance in including very high numbers of women with ovarian cancer and controls, thereby providing a high degree of statistical power.(39)

The 7 meta-analyses that I reviewed for this report included data from available cohort and case-control studies. I also reviewed the pooled analysis of 8 case-control studies.(39) In addition to effect measures (relative risks, odds ratios, hazard ratios) and their confidence intervals (or other test of statistical significance such as p-value), I reviewed the number of people with and without disease for each exposure category, method of exposure ascertainment, estimated exposure categories, assessment of dose-response effects, and effect sizes for all epithelial ovarian cancer and for subtypes of epithelial ovarian cancer (invasive, borderline, serous, endometrioid, mucinous, clear cell).

Possible Sources of Bias in Epidemiologic Studies Reviewed

All studies of all types must be criticality evaluated for both strengths and potential limitations in order to determine the totality of evidence. Limitations in epidemiologic studies are often characterized as biases. These include the biases listed below. It is important to note that the presence of bias does not render an epidemiologic study invalid. Rather, biases are issues that should be carefully considered when assessing how much weight should be given to individual studies, and what conclusions can be drawn from them.

Missing data: Both case-control and cohort studies can suffer from missing data. If the missing data items are related to the use of talcum powder products, then the estimated relative risks/odds ratios will likely be artificially low. If, in cohort studies, the cases of ovarian cancer are not identified, i.e., the cancer data are missing, the statistical power to detect statistically significant effects will be lessened. Both of these conditions would likely mean the true association between use of talcum powder products and risk of ovarian cancer is actually higher than what is observed in the epidemiologic studies.

Poor precision of exposure measurement: Determining whether, how much, and for how long women were exposed to talcum powder products is difficult. Women may not remember the brand of powder products they used, and contents of personal powder products may not be clear or may change over time. Women may not remember the amount of products used, frequency of use, and years of use.

Publication bias: The publication of epidemiologic studies depends on several factors. The investigators must have developed hypotheses about certain questions and designed the study accordingly, including asking the correct questions about the exposure and potential confounding variables, and collecting information from a sufficient number of participants. The investigators then need to perform statistical analyses, develop scientific manuscripts, and submit for journal publication. It may be difficult to find a journal that will accept null results (i.e. where an exposure is shown to not be related to an outcome).(48, 49) The pooled analysis of case-control studies provides some reassurance that publication bias is less likely for this association.(39) Of the 8 studies included in that analysis, 3 had not been previously published. Ever use of talcum powder products in the genital area produced odds ratios of 1.37 (95% CI 1.07–1.67), 1.36 (95% CI (1.06–1.74), and 0.99 (95% CI 0.70–1.41) for the 3 individual studies. That the confidence intervals overlapped, and that 2 of the 3 studies showed statistically significant associations, suggest low publication bias for the association between use of talcum powder products in the genital area and risk of developing ovarian cancer.

Cancer process affecting likelihood of exposure: If women used talcum powder products in the perineal area due to symptoms from an early cancer process, results of studies could be biased. Cohort studies often guard against this by eliminating cases that develop within a short time of study enrollment. Case-control studies guard against this by asking participants to recall exposures one or more years prior to their cancer diagnosis (and similarly ask controls to recall exposures at least one year prior to interview).

Confounding: Variables related to both use of talcum powder products and risk of ovarian cancer could mask the true relationship between these variables. Epidemiologists handle this by adjusting in the analysis for these potential confounding variables. All of the studies reviewed performed adjustment for several potential confounding variables. Those studies that presented both adjusted and unadjusted odds ratios/relative risks found little effect of confounding variables on these relationships.

Recall bias: For the case-control studies, media reports of associations between talc and ovarian cancer could have influenced cases such that they recalled use of talcum powder products to a greater degree than controls. However, the studies for which data collection pre-dated news reports of this association showed similar effects to those for which data were collected afterward. Thus, "recall bias" is unlikely to be an issue. As mentioned above, recall bias is a theoretical bias; studies that have investigated other sources of data on exposures have failed to confirm the presence of differential recall between cases and controls.(47)

Non-response bias: Case-control studies with low levels of response in cases or controls can be biased, in that the non-responding cases and controls could differ with respect to use of talcum powder products.

Differential results of cohort versus case-control studies: Ideally, results of case-control and cohort studies would be similar for the relationship between an exposure and risk of disease. However, there could be several reasons for discrepancy in results between case-control and cohort studies. The exposure measurement may differ in the two types of studies. For example, cohort studies may measure exposure at study entry without updating and without ascertaining lifetime exposure. The study would then have only one time point of an exposure that could significantly attenuate the observed associations between exposure and disease.

Population-based case-control versus hospital-based case-control studies: For some exposure-disease relationships, population-based case control studies are the most valid method of comparing risk for exposed versus non-exposed persons because the risks to public health can better be estimated. For others, however, hospital-based case control studies may provide important information because controls with illnesses may be more likely to recall exposures compared with healthy controls from the community, and therefore recall bias can be reduced.

Causal Inference in Epidemiology

The overarching goal of epidemiologic research is to determine likely causes of disease, in order to determine who is at risk for that disease and how to prevent the disease in individuals and populations. Much of epidemiologic observational research in cancer focuses on determining the *associations* between an exposure and an outcome. In other words, in a sample of individuals, are the number of persons exposed to an agent more likely to develop a cancer than those who are not exposed? There are several related questions. For example, will the persons who are exposed to a higher dose have an even greater risk than persons with little exposure? Will those exposed for a longer period of time have greater risk than those exposed for only a short time? Epidemiologists follow guidelines and logic in determining likelihood of an exposure causing cancer.(50) In addition to epidemiologic data, epidemiologists also consider plausible biological mechanisms to explain observed associations. The weight of evidence depends on the validity of the data as well as the clinical and biological evidence, if available, to explain these associations.

In epidemiology, and therefore in this report, a positive association means that the exposure in question increases risk for a disease or outcome. A negative association refers to an exposure decreasing risk for the outcome.

In 1965, English epidemiologist Sir Austin Bradford Hill attempted to describe several aspects of the causal relationship in a speech to the Royal Society of Medicine's newly-established Section of Occupational Medicine.(43) As Bradford Hill explained, this is not a checklist of factors to be counted: "What I do not believe—and this has been suggested—is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*."

These aspects of a causal relationship are:

Strength of the association. If the risk of developing cancer is several times higher in persons exposed to a toxic agent, that increases the likelihood of causality. It is not a necessary condition for establishing causality and providing recommendations for avoiding a potential cancer-causing agent, however.

Indeed, several carcinogens raise risk of cancer less than doubling of risk, but because of a high prevalence of exposure, can have major public health effects. Other exposures may be highly prevalent to certain groups such as factory workers; such exposures need to be minimized to meet government regulations for worker safety. Several examples follow:

Alcohol and risk for postmenopausal breast cancer: Risk for postmenopausal breast cancer increases by approximately 10% (a relative risk of 1.1) for each 10 gram/day intake of alcohol (the amount in a four-ounce glass of wine).(51) Women are advised to avoid alcohol or minimize alcohol intake to no more than one alcoholic drink per day to reduce risk for this cancer.(51) As Bradford Hill pointed out in his address: "We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so."(43)

Air pollution and risk for cardiovascular disease: A 2013 meta- analysis found that for each 10 μg/m3 rise in $PM_{2 5}$, the air pollution caused by motor vehicles, yields an 15% increase in risk of cardiovascular disease (similar to a relative risk of 1.15). Given the widespread prevalence of exposure to ambient pollution, even modest contributions to cardiovascular disease risk can have a substantial effect on population health. (52)

Outdoor particulate matter air pollution and lung cancer: A 2014 meta-analysis including 18 studies showed a relative risk of 1.09 (95% CI 1.04-1.14) per 10-$\mu g/m^3$ of exposure to particulate matter ($PM_{2.5}$).(53) This is highly significant, because 10-$\mu g/m^3$ of exposure to $PM_{2 5}$ is the lowest recommended limit set by IARC for minimizing health effects of air pollution.

Benzene at work and risk of leukemia: In 2010, a meta-analysis of 15 epidemiologic studies found that worksite benzene exposure increased risk of any leukemia by 40% (relative risk 1.40, 95% CI 1.23-1.57).(54)

Estrogen-progestin menopausal hormone therapy and breast cancer risk: The Women's Health Initiative clinical trial showed that this type of hormone therapy increases risk of breast cancer by 26% after an average 5 years of use. That level of risk was sufficient for clinical interest groups and governmental agencies to advise women to use hormone therapy for limited periods of time, if at all, because of risk

for breast cancer and other adverse events with similar levels of increased risk (29% increase in coronary heart disease, and 41% increase in stroke).(55) A meta-analysis of clinical trials and observational studies in 2018 found that use of this therapy increased risk of breast cancer by 59% (relative risk 1.59, 95% CI 1.40-1.81).(56) These results led to FDA-required label warnings on estrogen and progesterone therapy preparations(57), and to clinical warnings against use of estrogen plus progesterone for prevention of chronic conditions.(58)

Trichloroethylene and risk of kidney cancer: In 2012, a meta-analysis was published showing that occupational exposure to trichloroethylene was associated with an approximately 30% increased risk for kidney cancer (relative risk 1.32, 95% CI 1.17-1.50).(59)

Regular physical activity is associated with reduced risk for cardiovascular disease, diabetes, and various cancers in persons who meet national physical activity guidelines of 150 minutes/week of moderate-intensity aerobic activity.(60) In one large pooled analysis of 6 cohorts with 661,137 men and women, investigators found a 20% lower mortality risk among those performing less than the recommended minimum of 7.5 metabolic-equivalent hours per week (hazard ratio, 0.80 [95% CI, 0.78-0.82]), a 31% lower risk at 1 to 2 times the recommended minimum (hazard ratio, 0.69 [95% CI, 0.67-0.70]), and a 37% lower risk at 2 to 3 times the minimum (hazard ratio, 0.63 [95% CI, 0.62-0.65]).(61) To compare with the relative risks for adverse exposure, one would look at the inverse of the hazard ratios, i.e., 1.25, 1.45, and 1.59.

Intermittent intense sun exposure and risk of melanoma: A 2005 meta-analysis included data from 57 epidemiologic studies with 38,671 cases of melanoma, and found a relative risk of 1.61 (95% CI 1.31-1.99) for intermittent intense sun exposure.(62)

Prevention of skin cancer with use of sunscreen has also been observed, with similar effect sizes. In a 4.5-year trial with an additional 8-years follow-up, individuals randomly assigned to daily sunscreen use had almost a 40% reduced risk of squamous cell carcinoma (rate ratio, 0.62; 95% confidence interval, 0.38-0.99).(63) To compare with the relative risks for adverse exposure, one would look at the inverse of the risk ratio, i.e., 1.6.

Consistency of the association. A consistent association would be observed in various populations, places, circumstances, and times. Has the association been found in different countries, in persons from

various race/ethnic groups, and of different ages? This is also not a requirement, as there could be occasions when an exposure only increases risk for specific categories of individuals. An example, again from the breast cancer field, is that obesity increases risk for breast cancer occurring after menopause but decreases it for women who have not yet undergone menopause. Relevant to the association between ovarian cancer risk and use of talcum powder products, the association has been observed in the U.S., Canada, China, Australia, Israel, and the UK. While most data have been collected in Whites, a positive association between use of talcum powder products and risk for ovarian cancer has also been found in Blacks and Asians.

Specificity of the association: This suggests that if an exposure causes only one type of disease, that its causal link to that disease is strengthened. However, Bradford Hill recognized the limits of this aspect. One noxious agent, such as tobacco smoke, is an accepted cause of multiple cancers as well as cardiovascular disease. Similarly, one disease can have multiple causes. For example, lung cancer risk is increased with exposure to radon and asbestos, even in persons who do not smoke. In support of this, Bradford Hill stated, “One-to-one relationships are not frequent. Indeed I believe that multi-causation is generally more likely than single causation…”(43)

Temporality: The time course between exposure and disease occurrence is an important consideration. Bradford Hill was referring to the need to document that the exposure came before the disease, rather than something about the disease causing a person to come into contact with the exposure. This is why, for case-control studies, researchers have often queried women about their lifetime history of use of talcum powder products, beginning from young ages. Some cohort studies, on the other hand, asked about current use of these products when the women were first enrolled in the cohort. However, for all of these studies, only talcum powder product use prior to the cases’ diagnoses (and prior to a comparable time point for controls, in case-control studies) was counted as “exposure.”

Biologic gradient*:* This refers to the dose-response curve or the shape of the association between exposure and risk as the amount of exposure changes. If risk for a disease increases with increasing amount of exposure, the likelihood of a causal relationship is often increased. The exposure can be classified by total duration of exposure, by usual amount of exposure, or by a combination of these two. For use of talcum powder products, dose has been estimated by total years of use, by frequency of use, and by a combination of these two variables. It should be noted that ovarian talc particle burden may

not be influenced by number of applications of perineal talc usage(64), and therefore the typical dose-response relationship may not be necessary for establishing causality between perineal talcum powder product use and risk for ovarian cancer. Indeed, there are numerous substances for which there is no safe dose.

Plausibility: The association is strengthened if it is biologically plausible. However, Bradford Hill recognized that "What is biologically plausible depends upon the biological knowledge of the day." It is important to note that biologic plausibility does not require proof of mechanism.

Coherence: The cause-and-effect interpretation of the data should not significantly conflict with the known facts about the natural history and biology of the disease. Therefore, for example, the concurrent rise in tobacco smoking rates and rise in lung cancer incidence in the 20th century in the U.S., as well as the more recent concurrent decrease in smoking rates and decrease in lung cancer occurrence, strengthen the association between smoking and lung cancer as causal. For the case of use of talcum powder products and ovarian cancer risk, the prevalence of other risk and protective factors (e.g., use of oral contraceptives, hysterectomy, and tubal ligation as protective factors, obesity as risk factor) changed over time in the general population. Therefore, it would be difficult to determine if ovarian cancer incidence time trends vary by changes in use of talcum powder products. The biology involves, as described below, the migration of talc to the ovaries, the inflammatory process which talc elicits, and the carcinogenetic effects of inflammation.

Experiment: The evidence from randomized controlled trials can provide strong support to observational evidence. However, in many situations, randomized controlled trials are not feasible. In the case of talcum powder products and ovarian cancer risk, a trial would have to be very large, involving 50,000 women or more, followed for decades, to determine effects of use of talcum powder products on risk for ovarian cancer. This is because ovarian cancer is a rare disease and typically takes many years to develop to be clinically diagnosable. In addition, because the effects of genital talcum powder product use could be harmful, it would be unethical to conduct a trial of this type.

Analogy: Bradford Hill states that in some circumstances it would be fair to judge by analogy. Therefore, since some toxic agents such as thalidomide or rubella have been shown to cause birth defects, other drugs or viral exposures may be recognizable as possibly leading to harmful effects to a

fetus. Regarding talcum powder products use and ovarian cancer use: since increased inflammation has been associated with increased ovarian cancer risk, and since talc causes an inflammatory response in tissues, this strengthens the link between talcum powder products use and ovarian cancer risk.

Methods Used for this Review

In performing this evidence review and for purposes of my opinions, I first conducted a review of the relevant literature on the epidemiology of ovarian cancer risk in relation to use of talcum powder products, using the same process I use for systematic review articles I write for my academic work.(60, 65) I triaged articles by title, then by abstract, and finally by complete paper. As I read the epidemiologic literature, I considered the “Bradford Hill” aspects of causal inference(43), as well as causal inference as defined by Rothman(50), and weighed the evidence. My search identified studies that both support and do not support my eventual opinion on whether use of talcum powder products can cause ovarian cancer.

I searched in the PubMed database for research studies published in peer-reviewed, PubMed indexed journals, using the following search terms: (“talc” OR “talcum powder”) AND (“ovarian cancer” OR “ovarian carcinoma”).

The search produced 110 references, of which 7 included meta-analyses (11, 22, 34-38), one was a pooled analysis (39), and 33 were reports of original epidemiologic studies that tested the association between talcum powder products and risk of ovarian cancer.

I did not perform a meta-analysis, because excellent meta-analyses have been recently published,(34, 35) and all of the published meta-analyses showed similar relative risk estimates for use of talcum powder products and risk of ovarian cancer. For all of the reviewed studies, I performed data extraction using a standardized data extraction table (see Tables 1-4). I recorded information on the publication year, study design, number of cases, number of controls (for case-control studies), total sample size (for cohort studies), population type, country, risk estimates, confidence intervals, and the type of ovarian cancer. I also indicated whether dose-response relationships were assessed, method used, and results.

In this report, I provide descriptions of the study methods and main study results including risk estimates (odds ratio, relative risk, or hazard ratio). All studies included control for some confounders and presented the risk estimates with adjustment for the confounders. I present below the results from adjustment with the greatest number of variables.

Epidemiologic Evidence on the Association between Talcum Powder Products Use and Ovarian Cancer Risk

Case-control Studies

Schildkraut *et al*. (2016)(1) investigated the association between body powder use and ovarian cancer in African American women in 11 geographic areas of the U.S. Included were 584 cases and 745 controls, in a population-based study. Cases were identified through state or SEER cancer registries, or through hospital gynecologic oncology departments. Controls were randomly selected from the same populations as the cases. Participants were asked in a phone interview whether they had ever regularly used talc, cornstarch, baby, or deodorizing powders. Women were classified as "regular users" if they reported using any of these powders at least monthly for at least 6 months, and "never users" otherwise. Regular users were asked about frequency and duration of use; use on genital areas, underwear, sanitary napkins, or diaphragms; and use on non-genital areas. Lifetime number of applications was estimated as number of applications per month times number of months used. Occupational exposure (yes/no) was ascertained for a subset of participants. Use of genital powder was associated with a statistically significant 44% increased risk for ovarian cancer (odds ratio 1.44, 95% CI 1.11-1.86). A dose-response trend was noted: compared with never-users, women who used genital powder less than daily had a 12% increased risk for ovarian cancer, while women who used genital powder daily had a 71% increased risk. The statistical test for trend was significant ($p < 0.01$). Furthermore, a greater number of years used increased risk further: compared with never-users, women who used genital powders for less than 20 years had a 33% increased risk of ovarian cancer, while those who used genital powders for 20 years or more had a 52% increased risk of ovarian cancer. The statistical test for trend was significant ($p = 0.02$). Estimated lifetime number of applications was also related to risk in a dose-dependent manner. Compared with never users, those who used few than 3600 genital powder applications had a 16% increased risk for ovarian cancer, while those who used 3600 or

more applications had a 67% increased risk. The statistical test for trend was significant ($p < 0.01$). Risk of both serous and non-serous ovarian cancer increased statistically significantly with any genital powder use by 38% and 63%, respectively (odds ratios, 1.38, 95% CI 1.03-1.85, and 1.63, 95% CI 1.04-2.55, respectively).

Cramer *et al*. (2016) (2) reported on association between genital talc use and risk of ovarian cancer in 2,041 cases of ovarian cancer and 2100 controls. Cases were combined from three case-control studies interviewed in 1992-97, 1998-2002, and 2003-2008. Cases were identified from tumor boards and registries in Eastern Massachusetts and Massachusetts. Controls were identified from the same populations as controls. Interviewers asked participants if they “regularly” or “at least monthly” applied powder to the genital or rectal area, sanitary napkins or tampons, underwear, or non-genital areas. Type of powder, age begun, years used, and applications per month were ascertained. Lifetime exposure was estimated by multiplying frequency of applications per month by months used, and talc-years were calculated. Participants were then divided into quartiles according to these variables. Participants were also asked if their partners dusted or sprayed powder to their genital or rectal areas. Condom and diaphragm use were ascertained as potential sources of genital talc exposure. Genital talc use was associated with a statistically significant 33% increased risk of ovarian cancer (odds ratio 1.33, 95%CI 1.16-1.52). Risk decreased with increasing time since last use. There was a clear trend to increasing risk for ovarian cancer with increasing frequency of use: compared with never users, risks for 1-7 days per month, 8-29 days per month, and 30 or more days per month were increased by 17%, 37%, and 46%, respectively, and the trend was statistically significant ($p<0.0001$). Furthermore, as months per year of use increased, risk increased, and the trend was statistically significant ($p=0.006$). Risk for serous invasive, endometroid invasive, and serous borderline were increased with any genital talc use, by approximately 40%, and all were statistically significant. Risks of serous invasive and endometroid also increased significantly with increased talc-years of use. Risks of serous invasive were increased in both premenopausal and postmenopausal women who used genital products, but the results were only statistically significant in premenopausal women. Premenopausal women and postmenopausal women using hormone therapy had the largest risks associated with talcum powder product use for most types of ovarian cancers.

Wu *et al*. (2015) (3) investigated the associations of risk of ovarian cancer and talcum powder products use and other risk factors. Cases were identified through the SEER population-based University of

Southern California cancer registry. A total of 1,701 patients were included; and 2,319 controls were recruited from the cases' neighborhoods using random selection from population lists. In-person interviews were conducted. To determine use of talcum powder products, women were asked if they ever used talc at least once per month for 6 months or more.(6) If the response was positive, they were asked whether they had ever used talc in non-perineal areas (feet, arms, chest or back), perineal areas, or on underwear or sanitary pads/diaphragm. Questions on talc use included age at first use, frequency of use (times per month) and years of talc use. Use of genital talc for one year or more was associated with a statistically significant 46% increased risk for ovarian cancer (odds ratio 1.46, 95% CI 1.27-1.69). Similar relative risks were seen in non-Hispanic white, Hispanic, and African-American women. A dose-response analysis found that for each 5-year use of genital talc products, risk for ovarian cancer increased by a statistically significant 14% (95% CI 1.09-1.20).

Kurta *et al*. (2012)(4) published results of a population-based case-control study based in Western Pennsylvania, Eastern Ohio, and Western New York State. A total of 902 cases were enrolled, and 1,802 controls were randomly selected from the general population of those areas. Perineal talc use was defined as ever using dusting powder or deodorizing spray on the genital or rectal areas, on sanitary napkins, on underwear, or on diaphragms or cervical caps. Use of perineal talc increased risk for ovarian cancer by a statistically significant 40% (odds ratio 1.40, 95% CI 1.16–1.69).

Rosenblatt *et al*. (2011) (5) published results of a population case-control study set in western Washington that investigated the association between genital powder exposure and risk of ovarian cancer. A total of 812 women with ovarian cancer were identified through a population-based cancer registry and interviewed. A total of 1,313 controls were selected at random from the western Washington population. Sources of genital powder were ascertained, including direct perineal application, use on sanitary napkins and diaphragms, and use of deodorant vaginal spray. For powder use on sanitary napkins and use of vaginal deodorant sprays, the authors recorded the total number of months or years in which these products were used. For use of perineal powder, the investigators recorded the age began and ended, number of weeks or months of use per year, and average days per week used. Study participants were also asked about the types of powder used, including talcum, baby, cornstarch, deodorant, body/bath, and other or unknown. The authors then calculated the lifetime duration of use, and estimated lifetime number of applications. Perineal use of powder was associated with a non-statistically significant 27% increased risk for ovarian cancer (odds ratio 1.27, 95% CI 0.97-

1.66). The risk for borderline ovarian tumors was statistically significantly raised by 55% (odds ratio, 1.55, 95% CI 1.02-2.37), whereas risk for invasive ovarian cancers was increased by a non-statistically significant 27% (odds ratio 1.27, 95% CI 0.87-1.58). Use of powder on either sanitary napkins or diaphragms did not increase risk. Use of vaginal deodorant spray increased risk by a non-statistically significant 15% (odds ratio 1.15, 95% CI 0.85-1.56). None of the dose-response or time variables (years of use, lifetime number of applications, age at first use, age at last use, calendar year of first use, time since first and last uses) showed evidence of increasing relative risk of ovarian cancer with increasing level of exposure to talcum powder products. Similarly, there was no evidence of increased risk for ovarian cancer with increasing dose of powder use on sanitary napkins, or of vaginal deodorant sprays. Use of perineal powder increased risk for mucinous borderline, serous borderline, endometrioid, and other non-mucinous ovarian cancers by 47% to 78%, but none of the odds ratios was statistically significant.

Wu *et al.* (2009) (6) presented results of a case-control study of ovarian cancer with 609 cases and 688 controls. Risk of ovarian cancer among users of talcum powder products in the perineal area was increased by 53% (odds ratio 1.53, 95% CI 1.13-2.09). Risk of serous ovarian cancer was also significantly elevated (odds ratio 1.70, 95% CI 1.27-2.28). A statistically significant trend to increased risk with lifetime numbers of applications was observed. Compared with no use, odds ratios for those with $\leq$ 5200, >5200 - $\leq$15,600, >15,600 - $\leq$52,000, and > 52,000 applications were 1.2, 1.38, 1.34, and 1.99, respectively (p_{trend} = 0.0004).

Moorman *et al*. (2009) (7) published data from a population-based case-control study in White and Black women. In total, 1114 cases and 1086 controls were interviewed. They found no association of genital talcum powder product use and risk for ovarian cancer in Whites (odds ratio 1.04, 95% CI 0.82-1.33), and a non-statistically significant increased risk in Blacks (odds ratio 1.19, 95% CI 0.68-2.09). Neither dose-response nor effects by histologic subtype were addressed.

Merritt *et al*. (2008) (8) published results from an Australian-wide population-based case-control study on talcum powder products and risk of ovarian cancer. Included were 1,576 women with ovarian cancer and 1,509 population-based controls. Women provided information on self-administered questionnaires. They were asked if they had ever used powder or talc in the genital area, on underwear, or on sanitary pads or diaphragms. They were also asked about age at first use and years of talc use in

these areas. Duration of talcum powder use prior to and after surgical sterilization was calculated, and all analyses were limited to the time when the fallopian tubes would have been patent. Use of talc elsewhere was also collected. Ever use of talc in the perineal region was associated with a statistically significant 17% increased risk for ovarian cancer (odds ratio 1.17, 95% 1.01-1.36). The increase was strongest for serous (odds ratio 1.21, 95% CI 1.03-1.44), but was also seen for endometrioid (odds ratio 1.18, 95% CI 0.81-1.70). A statistically significant dose-response trend for years of perineal talcum powder use prior to surgical sterilization was seen for all cases combined (p=0.021) and for serous ovarian cancer (p=0.022). While not statistically significant, increasing years of use was associated with increased risk of mucinous and endometrioid ovarian cancers.

Mills *et al*. (2004) (9) reported on a population-based case-control study in 22 counties of Central California. A total of 256 cases were recruited from cancer registries and interviewed, and 1,122 population-based controls were randomly selected and interviewed. Women were asked the following about use of talcum powder: use in the genital area, years of use, frequency of use, and total duration of use. Ever use of perineal talc statistically significantly increased risk for ovarian cancer by 37% (odds ratio 1.37, 95% CI 1.02-1.85). There was a statistically significant trend found in the dose-response analysis of frequency of use; women using talc 4-7 times per week had a 74% increased risk for ovarian cancer (p=0.015). There was an indication of trend with duration of use up to 4-12 years, although number of years beyond that did not increase risk further. A similar relationship was found for cumulative dose (frequency times duration). Risk of serous ovarian cancer was also statistically significantly elevated (odds ratio 1.77, 95% CI 1.12-2.81).

Ness *et al*. (2000) (10) recruited women with ovarian cancer ascertained from 39 hospitals in Eastern Pennsylvania, Southern New Jersey, and Delaware. A total of 767 cases of ovarian cancer were interviewed, along with 1,367 population-based controls. Women were asked if they ever used talc, baby, or deodorizing powder at least once per month for 6 or more months in their genital or rectal area, on sanitary napkins, on underwear, on a diaphragm or cervical cap, or on non-genital areas. They also were asked about male partner use of talc to the genital area or underwear. Compared with never-users, women who used talc in genital/rectal areas had a statistically significant 50% increased risk for ovarian cancer (odds ratio 1.5, 95% CI 1.1-2.0). Those who used it on sanitary napkins had a statistically significant 60% increased risk for ovarian cancer (odds ratio 1.6, 95% CI 1.1-2.3). Use on underwear increased risk by a statistically significant 70% (odds ratio 1.7, 95% CI 1.2-2.4). Use on a

diaphragm/cervical cap or by a male partner did not increase risk. Among those who used in the genital/rectal or other body areas, there was no evidence of increasing risk with increasing numbers of years of use.

Cramer *et al.* (1999) (11) published results of a population-based case-control study with 563 cases of ovarian cancer and 523 controls. Risk of ovarian cancer among women with perineal talcum powder product exposure was increased 60% compared with non-exposed (odds ratio 1.6, 95% CI 1.18-2.15). Risk of invasive serous ovarian cancer was significantly increased (odds ratio 1.7, 95% CI 1.22-2.39). No dose-response effect, as defined by duration, was seen.

Wong *et al*. (1999)(12) conducted a hospital-based case-control study in Buffalo, NY, comparing 499 patients with ovarian cancer and 755 patients with non-gynecological malignancies. No details were given on how talcum powder product use was ascertained, but women were queried on site of talc use (sanitary napkin vs. genital/thigh area) and duration of use. Compared with non-users, those who used on sanitary napkins or genital/thigh areas had no increase in risk for ovarian cancer. Furthermore, there was no apparent trend toward greater risk with longer duration of use. Finally, there was a non-statistically significant 20% increased risk of serous ovarian cancer with talcum powder product use (odds ratio 1.2, 95% CI 0.7-2.1).

Godard *et al*. (1998)(13) studied risk of sporadic (101 cases) or familial (51 cases) ovarian cancer according to perineal talc use compared with 152 control in Montreal, Canada. Cases were diagnosed at one of two teaching hospitals; controls were randomly selected from the population. Talc use questions were not detailed in the paper, but the variable of "ever" versus "never" perineal use of talc was reported. Women who had ever used perineal talc had a 2.49 times greater risk of developing any ovarian cancer (relative risk 2.49, 95% CI 0.94-6.58, p=.066), which was marginally statistically significant. The relative risk for sporadic ovarian cancer was 2.45 (95% CI 0.85-7.07, p=0.098), and for familial ovarian cancer it was 3.25 (95% CI 0.85-12.4, p=.084).

Green *et al*. (1997)(14) included 824 Australian women with ovarian cancer who were identified through cancer registries, as well as 855 population-based controls. No details were provided on the specific questions posed regarding talc use, but perineal use was ascertained, as well as duration and ages/years used. Women who had ever used talc in the perineal region had a statistically significant 30% increased

risk for ovarian cancer (relative risk 1.3, 95% CI 1.1-1.6). The authors investigated whether a history of surgical sterilization affected this relative risk (the rationale being that women who are surgically sterilized would have lower chance of talc migrating up to the ovaries). They found that compared with women who had neither used talc nor had surgical sterilization, risk was highest among talc users without surgery (relative risk 1.3, 95% CI 1.0-1.7) and lowest among women with a history or tubal sterilization or hysterectomy who had not applied talc to the perineum (relative risk 0.6, 95% CI 0.5-0.84). No dose-response relationship by duration of use was found.

Cook *et al*. (1997) (15) reported on a population-based case-control study including 313 cases of ovarian cancer identified through a cancer registry and 422 population-based controls in Western Washington. Women were queried about storing diaphragms in powder, dusting perineal areas with powder after bathing, powdering sanitary napkins, and using genital deodorant sprays (which may contain aerosolized powder). Women were further asked about duration and frequency of powder application and about types of powder applied. There was a statistically significant 50% increase in risk of ovarian cancer associated with use of any of the genital powder applications (perineal application, sanitary napkins, genital deodorant sprays, diaphragms) (relative risk 1.5, 95% CI 1.1-2.0). The risk was highest, and statistically significant, in those women who dusted perineal areas with powder (relative risk 1.8, 95% CI 1.2-2.9). Compared with never users of genital deodorant sprays, women who used these products for 12 months or less had a relative risk for ovarian cancer of 1.5, while those who used them for more than 12 months had a relative risk of 2.7. Compared with never users of genital deodorant sprays, women who used 500 lifetime applications or less of genital deodorant sprays had a relative risk for ovarian cancer of 1.7, while those who used more than 500 applications had a relative risk of 2.6. Both of these dose-response trends were statistically significant ($p < 0.05$). None of the other types of perineal talcum powder product use showed trends to greater risk with greater estimated duration used or applications. The authors then categorized powders into specific types: cornstarch, talcum powder, baby powder, deodorant powder, and scented body/bath powder (assuming talcum powder was likely a constituent of the latter three as well). Exclusive use of cornstarch, or of deodorizing powder, was not associated with increased risk for ovarian cancer, but the numbers of cases were very small (5 and 9, respectively). Exclusive use of other types of powder increased risk between 20 and 60 percent, but the results were not statistically significant. Risk for serous ovarian cancers was statistically significantly increased by 70% in women who ever used any genital powder (relative risk 1.7, 95% CI 1.1-2.5). The relative risk for

"other tumors" among ever users was 1.8 (95% CI 1.1-2.8), while risks for mucinous or endometrioid tumors were not increased in genital powder users.

Chang *et al*. (1997)(16) reported on the association between talcum powder product use and risk of ovarian cancer in a population-based case-control study in Ontario, Canada. A total of 450 patients with borderline or invasive ovarian cancer and 564 population controls were interviewed. Women were asked about regular talc use and type of talc used, as well about duration and frequency of use. Women were queried about regular application of talc to the perineum and about use of talc on sanitary napkins. Use of cornstarch on the perineum and sanitary napkins was also ascertained. Women with any regular talc exposure had a statistically significant 42% increased risk of developing ovarian cancer (odds ratio 1.42, 95% CI 1.08-1.86). Use of cornstarch was not associated with increased risk, although this was a very uncommon exposure in this study. Use of talc on sanitary napkins increased risk to a lesser degree (odds ratio 1.26, 95% CI 0.81-1.96), as did use of talc only in the perineal area (odds ratio 1.31, 95% CI 1.00-1.73). A dose-response trend was seen: per 10 years of use of talc to the perineal area, risk of ovarian cancer increased by 6% (odds ratio 1.06, 95% CI 0.99-1.14). Frequency of use per month, however, did not show a dose-response trend. Use before and after 1970 showed almost identical odds ratios. Risk was higher prior to tubal ligation/hysterectomy than after either procedure. Risk was increased for all types of ovarian cancer included (invasive, borderline, serous, mucinous, and endometrioid). Only for invasive cancer was the odds ratio statistically significant, likely due to the larger numbers of cases in that category.

Shushan *et al*. (1996)(17) published results of a population-based case-control study in Israel, looking at the association between talcum powder product use and risk of invasive or borderline ovarian cancer. A total of 200 cases, identified through a cancer registry, were interviewed, as were 408 controls selected randomly from the same population. Details of the talcum powder product use on the standardized questionnaire were not provided. Women who reported using talc "moderate to a lot" versus "never or seldom" had twice the risk of developing ovarian cancer, and the result was statistically significant (odds ratio 2.0, p=0.04).

Purdie *et al*. (1995)(19) studied the association between talcum powder product use and ovarian cancer risk in 3 Australian states. Cases were recruited from registries at three oncology treatment centers, and controls were chosen randomly from the general population. The details of the interview items on talc

were not provided. Women who used talc around the perineum or abdomen had a statistically significant 27% increased risk for ovarian cancer (odds ratio 1.27, 95% CI 1.04-1.54).

Cramer *et al.* (1995)(18) published results of two case-control studies, in which a total of 450 women diagnosed with ovarian cancer in Boston, MA area hospitals, and 454 controls selected from the general population, were interviewed. Use of talc “in genital hygiene” was associated with a 60% increased risk for ovarian cancer (odds ratio 1.6, 95% CI 1.2-2.1).

Tzonou *et al*. (1993)(28) conducted a hospital-based case-control study in Athens, which included 189 women with ovarian cancer and 200 hospital visitor controls. No information was provided on how talcum powder product use was ascertained, other than that women were interviewed about whether or not they used of talc in the perineal area. There was little evidence of an association: the relative risk for ovarian cancer in those who said “yes” versus “no” to perineal talc use was 1.05 (95% CI 0.28-3.98). However, only 6 cases and 7 controls reported using talc in the perineal area.

Rosenblatt *et al*. (1992)(20) published results of a hospital-based case-control from the Baltimore, MD area. A total of 77 cases of ovarian cancer and 46 controls, who were treated for non-gynecologic/non-malignant diseases, were included. Participants were interviewed about presence and length of genital fiber and respiratory fiber exposure. Fiber exposure was defined as exposure to asbestos, talc, and fiberglass. Dose of exposure was calculated as number of years of each type of genital or respiratory exposures from all sources, and only exposure prior to tubal ligation (for women who had that procedure) was counted. Use of genital talc was associated with a 70% increased risk (odds ratio 1.7, 95% CI 0.7-3.9). Use of talc on sanitary napkins resulted in almost a 5-fold statistically significant increase in risk of ovarian cancer (odds ratio 4.8, 95% CI 1.3-17.8). Talc use on diaphragms tripled risk for ovarian cancer (odds ratio 3.0, 95% CI 0.8-10.8). The odds ratios for these latter two exposures were not statistically significant. Women who had exposure years above the median had more than double the risk of ovarian cancer compared with women with lower exposure years (odds ratio 2.4, 95% CI 1.0-5.8).

Chen *et al.* (1992)(21) interviewed 112 women with ovarian cancer and 224 community controls in China. No information was provided about how women were asked about talcum powder product use prior to 3 years before diagnosis (for cases) and a comparable date in controls. Seven cases and 5

controls reported using "dusting powder" to the lower abdomen and perineum for 3 or more months, giving a relative risk of 3.9 (95% CI 0.9-10.6).

Harlow *et al.* (1992) (22)published a case-control study with 235 cases of ovarian cancer and 239 controls. The authors found a 50% increased risk of ovarian cancer in women who had ever versus never used talcum powder products in the perineal area with marginal statistical significance (odds ratio 1.5, 95% CI 1.00-2.1). Risk of serous cancer was similarly increased (odds ratio 1.4, 95% CI 0.9-2.2). Risk by number of lifetime applications indicated a dose response effect. Compared with no use, odds ratios for those with < 1000, 1000 – 10,000, and > 10,000 were 1.3, 1.5, and 1.8, respectively (p_{trend} = 0.09).

Booth *et al*. (1989) (23) reported on a hospital-based case-control study conducted in 15 hospitals in the UK. A total of 235 cases with ovarian cancer and 451 controls were interviewed and asked about monthly experiences from age 16 to 45 years. Frequency of exposure to perineal talc was ascertained. Compared with never-users, women who used genital talc rarely, monthly, weekly, and daily, respectively, had relative risks for ovarian cancer of 0.9, 0.7, 2.0, and 1.3, respectively, and the trend was statistically significant (p=0.05). Cases and controls did not differ by percentage who stored diaphragms in talc.

Harlow *et al*. (1989)(24) interviewed 116 women with serous or mucinous borderline ovarian cancer identified through a Western Washington population-based cancer registry, as well a population-based sample of 158 control women. The authors used an open-ended question asking women to specify the types of powder they used for perineal application after bathing, on sanitary napkins, and on diaphragms. Powder was categorized as baby, deodorizing, other/unspecified talcum, or cornstarch. There was no association between perineal use in general and risk for borderline ovarian cancer, but women who reported using powder on sanitary napkins had a relative risk of 2.2 (95% CI 0.8-19.8) compared with nonusers. Women who used deodorizing powders had a statistically significant relative risk of 2.8 (95%CI 1.1-11.7). No data were presented on frequency or duration of use.

Whittemore *et al*. (1988)(25) included 188 ovarian cancer cases (identified through 7 hospitals in the San Francisco, CA area, and 539 controls (of which approximately half were hospital controls and half were population-based controls). Women were asked whether they had ever use talcum powder on the perineum, on sanitary pads, or on diaphragms, and about frequency and duration of use. Women who

reported using talcum powder to the perineum had a non-statistically significant 45% increased risk for ovarian cancer (relative risk 1.45, 95% CI 0.81-2.60). Use on sanitary pads was associated with a non-statistically significant 38% reduced risk, and use on diaphragms was associated with a non-statistically significant 50% increased risk. The relative risk for ovarian cancer increased with increasing applications of talc per month; relative to nonusers, the relative risk for 1-20 times per month was 1.27, and the relative risk for 20 or more times per month was 1.45. None of these values was statistically significant. The increased relative risk was apparent for women who had never had tubal ligation or hysterectomy, but not for women who had had one of these procedures. Compared with non-users, women with 1-9 years of use had a relative risk of 1.6 (95% CI 1.00-2.57), but women with greater years of use had only a relative risk of 1.11 (95% CI 0.74-1.65).

Hartge *et al*. (1983)(26) provided a brief report on a small hospital based case-control study of ovarian cancer, which included 135 cases and 171 controls from the Washington, DC area. No information was provided on how the talc exposure was ascertained. The authors found that women who reported genital talc use had a relative risk of 2.5 compared with never users (95% CI 0.70-10.0), but this analysis was based on only 7 cases and 3 controls.

Cramer *et al.* (1982) (27) published the first study to look at the association between talcum powder product use and risk of ovarian cancer. This population-based study found an odds ratio of 1.92 (95% CI 1.27-2.89) for ever use of perineal talcum powder products in the perineal area. Dose-response was not addressed.

Summary of Case-control Studies

These 28 case-control studies included population-based and hospital-based studies from a diverse geographic area across the U.S., as well as Australia, Canada, the UK, Israel, Greece, and China. Sample sizes ranged from 77 to 2041 cases, with comparable numbers of controls. Of the 28 studies, 24 found odds ratio greater than 1.1 for ovarian cancer in women who had any perineal exposure to talcum powder products, compared with never users(1-6, 8-11, 13-23, 25-27). Of these 24 odds ratio estimates, 16 were statistically significant (95% confidence intervals excluded 1.0 or p value $\leq$ 0.05)(1-4, 6, 8-11, 14-19, 27). Among the 8 studies which were not statistically significant, 7 had a sample size lower than that estimated to be needed to have power to detect a statistically significant result(13, 20-23, 25, 26). It is

important to note that while the 8 studies did not have statistically significant results, they provide relevant data because their relative risk estimates were consistent with the 16 studies that showed statistically significant results.(50)

Both population-based and hospital-based studies were represented in the literature on use of talcum powder products and risk of ovarian cancer, and odds ratios/relative risks were similar across the two classes of studies. Earlier studies were less likely to address dose-response relationships, or to investigate effects of talcum powder product use on specific histologic subtypes of ovarian cancer. Most studies were limited to white women; later studies included larger numbers of Black women as well as Asian and Latina women.

The larger, and more recent studies, however, added important information on dose-response relationships and on risk of particular histologic subtypes of ovarian cancer. Many of the 28 studies found evidence of a dose-response effect(1-3, 6, 8, 11, 20, 22, 23, 25). Most often, this took the form of lifetime numbers of applications of talcum powder products or years of use. The later studies determined that some risk of some subtypes, particularly serous ovarian cancer, were more highly related to use of talcum powder products.

Taken together, the case-control studies, conducted over 40 years, provide consistent and replicated evidence of increased risk of ovarian cancer with perineal exposure to talcum powder products, with evidence of a dose-response. They support the conclusion that talcum powder products can cause ovarian cancer.

Prospective Cohort Studies

The Sisters' Study

The Sisters' Study cohort analysis included 135 cases of women with ovarian cancer, 7 cases of fallopian tube cancer, 4 cases of peritoneal cancer, and 8 cases with unknown primary site. (30) Of the total 154 cases, only 96 were confirmed by medical records or death certificate. Women were recruited to the cohort from across the United States from 2003-2009. An analysis of talcum powder products use and ovarian cancer risk, published in 2016, included 41,654 women who reported having at least one ovary

and no history of ovarian cancer at study entry, from among 50,884 women aged 35-74 years at study enrollment with at least one sister who had been diagnosed with breast cancer.

Talcum powder products use for the 12 months prior to study entry was ascertained by self-administered questionnaires. Questions included frequency of genital talcum powder products use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Response categories were: did not use, used less than once a month, used 1-3 times/month, used 1-5 times/week, or used more than 5 times/week. Only a dichotomous variable—use/nonuse—was used in the analysis. Ovarian cancer cases were identified by yearly follow-up questionnaires; no updates on talc use were included. The median follow-up of study participants was only 6.6 years.

Contrary to all of the other epidemiologic studies, perineal talc use was associated with a non-statistically significant 27% decreased risk of developing ovarian cancer (hazard ratio 0.73, 95% CI 0.44 - 1.2). Of note, the 95% CI's included 1.2, so the true relative risk in this cohort could have been in the range of the other studies. Use of talcum powder products during ages 10-13 years showed a non-statistically significant 10% increase in risk (hazard ratio 1.1, 95% CI 0.74, 1.7). No data on risk by ovarian cancer subtype were presented.

Women's Health Initiative

In 2014, a report on the use of perineal powder in relation to ovarian cancer risk was published, using a total of 429 cases of women with ovarian cancer from the Women's Health Initiative cohort study.(29) Women were aged 50-79 years at study entry, and were recruited from 40 clinical centers across the United States between 1993-1998. While over 93,000 women were enrolled in the Women's Health Initiative cohort, this analysis included only 61,576. The largest number, 20,960, were excluded because they reported previously having had both ovaries removed or did not know whether they had any ovaries at the time of enrollment. Also excluded were 10,622 women with a history of any invasive cancer at enrollment. A further 516 were missing follow-up information. At study entry, women reported use of perineal powder on self-administered standardized questionnaires, in which they were asked if they had ever used powder on their genital areas. Those who responded yes were then asked to indicate if they used them for less than 1 year, 1-4 years, 5-9 years, or 20 or more years. Women who reported ever using a diaphragm were asked if they used powder on the diaphragm, and for what

duration. Women were also asked if they used powder on a sanitary napkin/pad, again with questions about duration. Because of the relatively small number of ovarian cancer cases (429) that occurred during the study, the investigators combined the duration categories into never, 9 years or less, or 10 years or more. The investigators then created one variable by combining the perineal use, diaphragm use, and sanitary napkin use, with duration as the maximum duration for any of the 3 application areas. Cases of ovarian cancer were identified by participants on annual follow-up questionnaires; no updates on talc use were included. Medical records and pathology reports were requested for each self-reported case and were adjudicated by clinic physicians and central cancer adjudicators. A total of 429 cases were included in the analysis.

Ever use of perineal powder was associated with a non-statistically significant 6% increased risk of ovarian cancer compared with never use (hazard ratio 1.06, 95% confidence interval 0.87 - 1.28). Risk of serous invasive cancer was increased by a non-statistically significant 13% (hazard ratio 1.13, 95% CI 0.84 - 1.51). Both of these results, while not statistically significant, are consistent with an association between talcum powder product use and risk of ovarian cancer overall and of serous ovarian cancer.

Nurses' Health Study

The Nurses' Health Study is a cohort established in 1976 that had 307 cases of ovarian cancer at its initial publication in 2000; further data with a total of 210 cases were published in 2008; and an unknown number of cases were analyzed for publication in 2010. The study initially enrolled 121,700 registered nurses between the ages of 30-55 years from across the United States. Use of talcum powder was ascertained on the self-administered 1982 questionnaire only, by asking women if they had ever commonly used talcum, baby powder, or deodorizing powder on their perineal areas. Possible responses were: no, daily, 1-6 times per week, or less than once per week. Women were also asked if they had applied these products to sanitary napkins. "Ever talc use" was classified as ever talc use on either the perineal area or sanitary napkins. Every two years, participants reported health updates; no updates on talc use were included, but self-reported cases of ovarian cancer were adjudicated through medical record reviews. Women were excluded from talcum powder products analyses if they did not complete the information on the 1982 questionnaire, if they reported having had both ovaries removed, if they had had a hysterectomy but did not report whether or not they had at least one ovary remaining, or if they had a history of radiation therapy.

There have been three publications from the Nurses' Health Study on the relationship between talcum powder products and risk for ovarian cancer.(31-33) The first, published in 2000, included 78,630 women, of whom 307 cases of ovarian cancer were diagnosed during a 14 year follow-up period. Ever use of talc was reported by 40.4% of the cohort; 14.5% ever used talc daily.(31)

The risk of ovarian cancer was not statistically significantly associated with epithelial ovarian cancer overall (relative risk 1.09, 95% CI 0.86-1.37), and risk did not increase with increasing frequency of use. Risk of serous ovarian cancer, however, was statistically significantly increased by 40% in women who had ever used talc (relative risk 1.4, 95% CI 1.02-1.91).

The second report from the Nurses' Health Study was in 2008.(32) In this study, 210 cases and a random sample of 600 controls from the Nurses' Health Study were combined with cases and controls from other case-control studies. Among the Nurses' Health Study cases and controls, the relative risk for ovarian cancer was 1.24 (95% CI 0.83-1.83).

Daily use was associated with a 44% increase in risk (relative risk 1.44, 95% CI 0.88-2.37), although neither association was statistically significant. Given that only 210 Nurses' Health Study cases were included, the lack of statistical significance is likely due to this insufficient sample size.

The third Nurses' Health Study report was published in 2010.(33) This report looked at multiple menstrual, hormonal, health habits, and familial risk factors for ovarian cancer; the variable on use of talc to the perineal area was limited to a dichotomous "greater than or equal to once per week vs. less than once per week)".

Use of talc one or more times per week compared with less use was not statistically significantly related to risk for epithelial ovarian cancer (relative risk 1.06, 95% CI 0.89-1.28), serous invasive (relative risk 1.06, 95% CI 0.84-1.35), or for other subtypes including endometrioid, or mucinous ovarian cancer.

It is difficult to compare the results of these three Nurses' Health Study publications. The first and third used different categories of use as the referent (comparison) group. The first publication used "never use" as the comparison and found a statistically significant effect for risk of serous ovarian cancer with

any use of talcum powder products. The third publication combined “never use” and “less than once per week” into one referent category. If low frequency use increases risk of ovarian cancer, which is entirely plausible, combining such women with never users will seriously underestimate the true relative risk associated with use of talcum powder products. The second publication found increased risks of total and serous ovarian cancer with use of talcum powder products, but the numbers were small and therefore the results were not statistically significant.

Cohort Studies Analysis

Two of the three cohort studies found small increases in risk of ovarian cancer overall among women who used talcum powder products in the perineal areas. The results were not statistically significant for ovarian cancer overall, however, likely due to insufficient sample size or incomplete ascertainment of talc exposure. The first Nurses’ Health Study publication found a statistically significant association between ever versus never use and risk of serous ovarian cancer. The Sisters’ Study found a reduced risk of ovarian cancer but did not report data by histologic subtype of ovarian cancer. Similar to the Nurses’ Health Study, the Women’s Health Initiative found an increase, albeit non-statistically significant, in risk of serous ovarian cancer in users versus nonusers of talcum powder products.

There were serious limitations to these cohort study analyses. None of the studies were specifically designed to investigate the relationship of talcum powder product use and risk of ovarian cancer. Rather, the cohorts were designed to study a large number of outcomes and a wide variety of exposures. Thus, none of the studies obtained detailed lifetime histories of talcum powder product use, although two did ask about duration of use for current users. None, therefore, was able to accurately measure dose of exposure. The sample sizes (numbers of cases) of most of the cohort study publications were likely too small to be able to detect a relative risk in the order of 1.24 (the value found in the Terry pooled analysis(39)) with reasonable power, especially for different histologic subtypes.

To assess likelihood of inadequate sample sizes in these cohort studies, I used an online calculator: http://www.openepi.com/SampleSize/SSCohort.htm. I used WHI data(29) to estimate the cohort sizes needed to determine a true relative risk of 1.24 (i.e. the relative risk from Terry et al pooled analysis(39)) with 50% exposure to talcum powder products in non-cases, and an assumption of 0.5% occurrence of ovarian cancer in unexposed women(66) over 12 years’ follow-up (the mean number of years of follow-

up in the WHI publication). My calculations show that to have sufficient power to identify a statistically significant relative risk of 1.24, the necessary cohort size would be over 140,000. None of the 3 cohorts had this large a sample size for these publications. Sample size ultimately rests on the numbers of cases that occur, rather than the actual cohort size. While the third Nurses' Health Study publication(33)—had a large sample size of cases, the authors' choice to combine never users with less than once per week users could have significantly attenuated the relative risk estimates.

Results of the cohort studies were overall attenuated compared with results of the case-control studies. However, the trend for 2 of the 3 studies was a positive relative risk of talcum powder product use and risk of ovarian cancer. In the Nurses' Health Study, women who used these products had a statistically significant 40% increased risk of developing serous invasive ovarian cancer compared with non-users.(31) In that study, use in the perineal area directly or on sanitary napkins increased risk of ovarian cancer overall by a non-statistically significant 15%.

In the Women's Health Initiative, use of talcum powder products to the genital area (or on sanitary napkins or diaphragm) increased risk overall by a non-statistically significant 6%, and risk of serous invasive ovarian cancer by a non-statistically significant 13%.

The Sisters Study asked only about use of talcum powder product use in the 12 months prior to enrollment; just 14% of the cohort used these products in that period. The cohort included only women at high risk for breast cancer recruited beginning in 2003—this may have been a group of women who were aware of the potential carcinogenic effect of talc, and therefore avoided use. This cohort study found a non-statistically significant 27% lower risk of developing ovarian cancer in users versus non-users. Given the likely 30-50-year latency of ovarian cancer development after exposure to a carcinogen(67), however, these results of the Sisters' Study are not likely reflective of risk from exposure to talcum powder products.

It is important to note that the effect sizes in the Nurses' study and in the Women's Health Initiative were in the same direction as seen in virtually all of the case-control studies.

Therefore, the attenuated results from these cohort studies do not reduce my confidence in the observations from the 28 case-control studies described above.

In summary, while the cohort studies on average showed more attenuated relative risks of ovarian cancer in relation to use of talcum powder product use, their results as a group do not negate the significant case-control study findings and the significant results of the meta-analyses and the pooled analysis.

Meta-Analyses and Pooled Analyses

I reviewed 7 meta-analyses (11, 22, 34-38) and one pooled analysis (39). All of the meta-analyses, and the pooled analysis, found summary elevated risks for ovarian cancer associated with use of talcum powder products. These elevated relative risks were statistically significant. Although many of the source studies from which they performed their meta-analyses had elevated risks for ovarian cancer with use of talcum powder products, the relative risks or odds ratios were not all statistically significant. I interpret the lack of statistical significance in some source studies as being due to the small sample sizes of many of these studies. I calculated the sample size required for a study in which 40% of controls used talcum powder products, in which there is good power (80%) to detect a relative risk of 1.3, and that had low chance of estimated a particular relative risk by chance (http://www.openepi.com/SampleSize/SSCC.htm). The calculation showed that the minimum number of cases and controls would need to be 931 each, for a total sample size of 1862. Almost none of the case-control or cohort studies had sample sizes this large. Lack of statistical significance found in the various studies is likely due to their small sample sizes. For this reason, evaluation of the meta-analyses and pooled analysis, with their larger sample sizes, is critical to understanding the state of epidemiologic evidence linking use of talcum powder products to risk of ovarian cancer.

Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-analysis (R. Penninkilampi, Eslick GD, 2018)

In this, most recent, meta-analysis and systematic review, the authors searched 6 electronic databases, and selected observational studies with at least 50 cases of ovarian cancer.(34) They analyzed the association between ovarian cancer, including specific sub-types, and the following variables regarding talcum powder products: any perineal talc use, long-term (> 10 years) use, total lifetime applications, and use on diaphragms or sanitary napkins. Included were 24 case-control studies, with 13,421 ovarian

cancer cases. Also included were three cohort studies, with 890 cases and a comparison of 181,860 person-years [numbers of non-cases multiplied by the years of follow-up]).

The authors found that any perineal talc use was associated with a statistically significant 31% increased risk for ovarian cancer (odds ratio 1.31, 95% CI 1.24-1.39).

There was evidence of a dose-response effect by number of lifetime applications. Women whose lifetime applications totaled less than 3600 had a statistically significant 32% increased risk of developing ovarian cancer (odds ratio 1.32, 95% CI 1.15-1.50), while those whose lifetime applications totaled over 3600 had a statistically significant 42% increased risk for ovarian cancer (odds ratio 1.42, 95% CI 1.25-1.61).

Increased risks were seen for all types of ovarian cancer, as well as specific subtypes: all serous (odds ratio 1.32, 95% CI 1.22-1.43), serous invasive (odds ratio 1.32, 95% CI 1.13-1.54), serous borderline (odds ratio 1.39, 95% CI 1.09-1.78), and endometrioid (odds ratio 1.35, 95% CI 1.14-1.6). For all of these subtypes, the confidence intervals did not include 1.0, and therefore are considered statistically significant and unlikely to be due to chance findings. For other subtypes, the following non-statistically significant associations were seen: all mucinous (odds ratio 1.12), mucinous invasive (odds ratio 1.34), mucinous borderline (odds ratio 1.18), and clear cell (odds ratio 1.02).

The association between ever use of talc and overall ovarian cancer risk was higher in case-control studies (odds ratio 1.35, 95% CI 1.27-1.43) than in cohort studies (odds ratio 1.06, 95% CI 0.90-1.25). However, the results for case-control and cohort studies were similar for serous ovarian cancer. In cohort studies, risk for serous invasive cancer was statistically significantly increased by 25% with any perineal talc use (odds ratio 1.25, 95% CI 1.01-1.55), and in case-control studies, it was statistically significantly increased by 36% (odds ratio 1.05-1.75). There was insufficient information from the cohort studies to calculate the dose-response variable (total lifetime applications).

In my opinion, the results of this 2018 meta-analysis give strong support for an association between perineal talcum powder product use and risk for ovarian cancer. A significant number of the aspects of the causal relationship that Bradford Hill describes in his address are present in these data, including strength, consistency, temporality, and biologic gradient. Bradford Hill did not define his first aspect—

strength—other than to say that the likelihood of causality is greater if the agent causes a "several fold higher" increase in risk in exposed persons. However, for agents like perineal talcum powder products that have such high prevalence of use (over 50% in some populations), the odds ratio/relative risk/hazard ratio for perineal talc use is of great importance for both public health and clinical medicine because it means that perineal talc use causes a significant number of ovarian cancer cases every year.

The corollary example of combined estrogen plus progesterone menopausal hormone therapy and breast cancer risk is helpful here. The Women's Health Initiative clinical trial showed that this type of hormone therapy increases risk of breast cancer by 26% after an average 5 years of use. That level of risk was sufficient for clinical interest groups and governmental agencies to advise women to use hormone therapy for limited periods of time, if at all, because of risk for breast cancer and other adverse events with similar levels of increased risk (29% increase in coronary heart disease, and 41% increase in stroke).(55) Further examples of relative risks less than 1.5 that have significant public health impact because of high prevalence of exposure in the population or in specific subgroups are shown on pages 26-27.

Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis (Berge W, Mundt K, Luu H, Boffetta P, 2017)

The authors of this meta-analysis performed a systematic search of PubMed, Embase, and Scopus databases(35). After quality assurance and redundancy checks, they included in their analysis 24 case-control studies and 3 cohort studies that reported on the association between talcum powder products and risk of developing ovarian cancer. The main meta-analysis compared ever versus never use of genital talc. Additional analyses looked at use of powder on sanitary napkins and diaphragms. Stratified analyses were conducted for tumor types.

From the meta-analysis, the authors observed a statistically significant 22% increased risk of developing ovarian cancer in women who had ever used genital talc versus never users (relative risk 1.22, 95% CI 1.13-1.30).

Significant results were found for dose-response relationships, both for number of years of use and for number of applications. Each 10-year increase in genital talc use was associated with a 16% increase in

risk for developing ovarian cancer (relative risk 1.16, 95% CI 1.07-1.26). Furthermore, each increase of one application per week was associated with a 5% increase in risk (relative risk 1.05, 95% CI 1.04-1.07).

Risk of serous carcinoma was the only subtype of ovarian cancer for which risk was elevated, and it was statistically significant (relative risk 1.24, 95% CI 1.15-1.34). “Late” exposure, which the authors hypothesized could be less likely to include asbestos, conferred a higher risk (relative risk 1.31, 95% CI 1.03-1.61) than did “early” exposure (relative risk 1.18, 95% 0.99-1.37). Neither specific use on a sanitary napkin nor on a diaphragm increased risk. Ever use of genital talc on a diaphragm was associated with decreased risk (relative risk 0.75, 95% CI 0.63-0.88).

The association of talcum powder use with increased risk of ovarian cancer was seen in case-control studies (relative risk 1.26, 95% confidence interval 1.17-1.35) but not in cohort studies (relative risk 1.02, 95% confidence interval 0.85-1.2). Furthermore, hospital-based case-control studies had a higher summary relative risk compared with population-based case-control studies (relative risks 1.34 and 1.24, respectively, both statistically significant).

In my opinion, the results of this meta-analysis are very similar to those of the later one described above, and further support the causal effect on ovarian cancer of talcum powder products applied in the perineal area.

Perineal Use of Talc and Risk of Ovarian Cancer (Langseth, Hankinson, Siemiatycki, Weiderpass, 2017)

In a meta-analysis conducted by some of the researchers who had investigated the epidemiologic research on talc exposure and ovarian cancer risk for IARC, data from 20 case-control studies were combined into a meta-analysis.(36) The authors found an overall odds ratio of 1.35 (95% CI 1.26-1.46) for ever- versus never-use of talcum powder products. The authors did not perform dose-response analyses.

Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from Sixteen Observational Studies. (Huncharek, Geschwind, Kupelnick, 2003)

This meta-analysis included fifteen case-control and two cohort studies that had been published between 1966 and early 2001, and that fit eligibility criteria, including documenting type of talc exposure (e.g. dusting perineum vs. sanitary napkins). The meta-analysis produced a statistically significant relative risk of 1.33 (95% confidence intervals 1.16-1.45) for ever versus never use of talc in the perineal area.(37)

The investigators addressed dose-response in the seven studies with information on years of talc exposure or numbers of talc applications per month. However, the authors combined categories of dose (applications per month) and duration of use (years) into one variable, and treated the dose-response analysis as if dose and duration were measuring the same construct. Their statement of lack of dose-response effect, therefore, is misleading in my opinion. The authors suggest that perhaps talc use has a similar carcinogenic effect as asbestos, and cites research showing that asbestos does not show a clear dose-response effect on risk of mesothelioma.

The authors also separated the results of hospital-based (e.g. both cases and controls from the same hospitals) from non-hospital-based (controls selected from the general population) and found a lower relative risk for ovarian cancer (1.19, not statistically significant) for the hospital-based studies and 1.38 (statistically significant) for population-based studies. The authors state that the hospital-based studies would be more accurate because they eliminate bias from case referral patterns to particular hospitals. However, many of the non-hospital-based studies used population-based case ascertainment (e.g. cancer registries) and selected population-based controls, which also eliminates the potential bias of hospital referral patterns.

Genital Talc Exposure and Risk of Ovarian Cancer (Cramer, Liberman, Titus-Ernstoff, Welch, Greenberg, Baron, Harlow, 1999)

In a paper that presented data for a case-control study of genital talc exposure and risk of ovarian cancer, Cramer et al. presented results of a meta-analysis of previous publications on the relationship between talcum powder product use and risk of ovarian cancer.(11) The authors included results from

14 case-control studies, from which they found a statistically significant combined odds ratio of 1.36 (95% confidence interval 1.24-1.49).

A Meta-Analytical Approach Examining the Potential Relationship between Talc Exposure and Ovarian Cancer (Gross and Berg, 1995)

In a meta-analysis sponsored by the Johnson and Johnson company, Gross and Berg included nine case-control and one cohort study in a meta-analysis, and found that the relative risk for women "exposed" versus "non-exposed" to talc was a statistically significant 1.27 (95% confidence interval 1.09-1.48).(38) Eliminating studies that included non-epithelial ovarian tumors, and studies that did not adjust for potential confounders, the relative risk remained statistically significant (relative risk 1.29, 95% confidence interval 1.02-1.63).

Perineal Exposure to Talc and Ovarian Cancer Risk (Harlow, Cramer, Bell, Welch, 1992)

Harlow and colleagues presented results of a meta-analysis of previous publications on the relationship between talcum powder product use and risk of ovarian cancer (in the same paper in which they presented data on a case-control study of ovarian cancer risk in relation to perineal talcum powder product exposure).(22) The authors included results from 6 case-control studies, from which they found a statistically significant combined odds ratio of 1.3 (95% confidence interval 1.1-1.6).

Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls (Terry KL *et al.*, 2013)

This pooled analysis used resources and data from the Ovarian Cancer Association Consortium, including 8 population-based case-control studies with relevant data on talcum powder product use.(39) Six of the studies were conducted in the U.S.(5, 7, 11, 68-70), one in Australia(8), and one in Canada(16). The analysis included 8,525 cases of ovarian, fallopian tube, or peritoneal cancer and 9,859 controls selected from the general population. Five of the studies had previously reported on use of talcum powder product and risk for ovarian cancer (5, 7, 8, 11, 16). To harmonize data on genital powder use across the studies, Terry *et al*. defined genital powder use as any type of powder (talc, baby, deodorizing,

cornstarch, or unspecified/unknown) applied directly or indirectly (by application to sanitary pads, tampons, or underwear) to the genital, perineal, or rectal area. Study-specific powder questions varied in detail about type and method of application. However, the authors were able to classify women into those who "ever used" genital powders vs. those who "never used" powders in the genital area. The included studies also had extensive data on other suspected risk factors for ovarian cancer that were adjusted for in the analyses. To measure cumulative dose of genital powder use, the authors estimated lifetime number of powder applications by multiplying total months of use by frequency of use per month.

Genital powder use was reported by 25% of controls and 31% of cases. In the pooled analysis, ever use of genital powder was associated with a statistically significant 24% increased risk of ovarian cancer (odds ratio 1.24, 95% CI 1.15-1.33) versus women who never used these products. In contrast, women who had used powders only in non-genital areas had no increase in risk for ovarian cancer. Risk for several subtypes of ovarian cancer was statistically significantly increased in women who had used genital powders. Risk for invasive serous cancer was increased by 24% (1,952 cases; odds ratio 1.24, 95% CI 1.13-1.35). Risk for endometroid cancer was increased by 20% (568 cases; odds ratio 1.2, 95% CI 1.03-1.4), and risk for clear cell cancer was increased by 26% (327 cases; odds ratio 1.26, 95% CI 1.04-1.52). Risk of serous borderline cancer was increased by 45% (odds ratio 1.45, 95% CI 1.24-1.69). Risk of mucinous cell invasive cancer and mucinous cell borderline cancer were not statistically significantly associated with use of genital powder products (206 cases; odds ratios 1.06, 95% CI 0.82-1.26; and 409 cases; 1.19, 95% CI 0.98-1.43, respectively).

There was a striking similarity in findings across studies, and the statistical test for heterogeneity was not significant ($p > 0.61$). All but one study showed odds ratios greater than 1.0, of which 5 were statistically significant (i.e., the confidence intervals did not contain 1.0).

To assess dose-response effects, the authors categorized participants who had used genital powder into 4 equal groups by lowest to highest level of use (quartiles), and compared their risk for ovarian cancer to that in non-users. A clear dose-response trend was evident. Compared with never users of genital powder, women in quartile 1 had a 14% increased risk for ovarian cancer (odds ratio 1.14, 95% CI 1.00-1.31), women in quartile 2 had a 23% increased risk for ovarian cancer (odds ratio 1.23, 95% CI 1.08-1.41), women in quartile 3 had a 22% increased risk for ovarian cancer (odds ratio 1.22, 95% CI 1.07-

1.40), and women in quartile 4 had a 32% increased risk for ovarian cancer (odds ratio 1.32, 95% CI 1.16-1.52). Slightly higher odds ratios were seen when the cancers were restricted to non-mucinous subtypes (i.e., serous invasive, endometroid invasive, clear cell invasive, and serous invasive): 1.18, 1.22, 1.22, and 1.37, respectively, for increasing levels of use by quartiles. When all 5 categories were included, the trend was highly statistically significant ($p_{trend} < 0.0001$).

The authors performed some additional analyses to make sure that the results were not biased. First, they excluded cases and controls who only began to use genital powders after undergoing tubal ligation or hysterectomy (after which powder likely would not migrate to the ovaries). This had no effect on the odds ratios—the increased risks for ovarian cancer remained virtually identical in each quartile. They then looked at effect of genital powder use and ovarian cancer risk by subgroups of women according to other ovarian cancer risk factors. They found no significant interactions between genital powder use and parity, reported history of endometriosis, tubal ligation/hysterectomy, or menopausal status. They did find that the effect of genital powder use was higher in normal/overweight women (odds ratio 1.28, 95% CI 1.17-1.39) than it was in women with obesity (odds ratio 1.14, 95% CI 0.98-1.32).

Finally, the authors looked at associations between genital powder use and ovarian cancer by years of beginning use. They found that the association between genital powder use and ovarian cancer risk was similar for women who started use between 1952 and 1961 (odds ratio 1.36, 95% CI 1.19–1.56), between 1962 and 1972 (odds ratio 1.27, 95% CI 1.11–1.46), and after 1972 (odds ratio 1.31 95% CI 1.15–1.51). However, they observed an attenuated association for women who started genital powder use before 1952 (odds ratio 1.08, 95% CI 0.93–1.25).

The Terry *et al.* pooled analysis provides strong evidence that perineal talcum powder product use causes ovarian cancer. “Strong” here does not pertain to size of the odds ratio/relative risk. Rather, it refers to the fact that the number of cases included was larger than any previous study, the 8 case-control studies included showed similar effect sizes for association of genital powder use and ovarian cancer risk (consistency), the dose-response effect was clear, and there were enough numbers of cases to determine effects on subtypes of ovarian cancer.

Summary of Meta-analyses/Pooled Analysis Results

All of the meta-analyses and the pooled analysis demonstrate increased risk of ovarian cancer in women who used talcum powder products in the genital or perineal area compared with nonusers. The earlier meta-analyses included fewer studies, primarily case-control studies. The most recent meta-analyses included three cohort studies and 24 case-control studies.(34, 35) The summary relative risks were quite consistent across the meta-analyses and the pooled analysis, ranging from 1.22 to 1.4 for any versus no use of perineal talcum powder products. Furthermore, all of the summary results were statistically significant. Importantly, the later meta-analyses(34, 35) and the pooled analysis(39) assessed dose-response relationships, while earlier meta-analyses did not(11, 22, 36), or did so inaccurately(37). These findings of increased risk of ovarian cancer with perineal exposure to talcum powder products shows that the observed associations overall and those for dose-response are robust.

One striking observation across the meta-analyses and pooled analysis is that the total sample sizes (numbers of cases) in all of the meta-analyses and the pooled analysis were sufficient to detect statistically significant relative risks of 1.3 for an overall “exposed” versus “non-exposed” variable with prevalence of 40 percent (see page 48 for a calculation of needed sample size). As shown in Tables 3 and 4, the numbers of cases in the meta-analyses and pooled analysis ranged from 1106 to 14,311, with controls of equal or greater number. All of these, therefore exceed the sample size I estimated that is needed to have statistical power to determine relative risks of 1.3. In contrast, many of the individual case-control or cohort studies did not have large enough samples of cases to have statistical power to determine a relative risk of 1.3.

Asbestos, Fibrous Talc, and Heavy Metals in Talcum Powder Products

It is important to note that talc is not asbestos-free. Talcum powder products contain other, potentially carcinogenic substances; of greatest concern is the presence of asbestos in talc, and the presence of talc with asbestiform fibers (fibrous talc), in these products. The presence of any one of these constituents add to evidence of biologic plausibility that would support the consistent increased risk seen in the epidemiologic studies.

Asbestos can take several forms. Proven carcinogenic forms include serpentine (chrysotile) and amphibole (actinolite, amosite, anthophyllite, crocidolite, and tremolite) minerals.(40) Both serpentine and amphibole asbestos forms are classified by IARC as Class 1 carcinogens(40). In their 2012 report, IARC stated that talc deposits may include tremolite, anthophyllite, and actinolite forms of asbestos(40).

Talc may form true mineral fibers that are asbestiform in habit. This form of talc is also referred to as fibrous talc and classified by IARC as a Class 1 human carcinogen(40). The IARC report also noted that "talc containing asbestiform fibers" is not the same as "talc contaminated by asbestos"(40). The conclusions reached in the 100c monograph about asbestos apply to fibrous talc (40). IARC has classified platy (non-fibrous) talc as a 2B "possible" carcinogen(42).

The primary route of exposure to asbestos is respiratory in the general population, although exposure through drinking water and exposure to hair or clothing of asbestos workers has also occurred (40). For talc, the primary exposures listed by the IARC report are respiratory and perineal (40).

Asbestos has been established as a cause of several types of cancer including epithelial ovarian cancer (40, 41). In order to assess the causal relationship between asbestos and ovarian cancer, I conducted a literature search. My search yielded a total of 26 studies that have investigated the epidemiology of asbestos exposure and risk of ovarian cancer. Two of these were meta-analyses, both published in 2011.(71, 72) One was a pooled analysis of 43 Italian cohorts with high asbestos exposure. (73) In addition, IARC published monographs on the carcinogenic role of asbestos, and conducted a systematic review through 2009 of asbestos and risk of ovarian cancer. (40, 41, 74) IARC concluded that asbestos, fibrous talc, chromium, and nickel are Group 1 human carcinogens.(40) IARC also classified cobalt as a 2B "possible" carcinogen.

Published data as recently as 2014 have shown that present-day talcum powder products include several types of asbestos.(75, 76) Company documents and testimony also provide further evidence of the presence of asbestos, fibrous talc, and heavy metals in talcum powder products.(77, 78) Dr. William Longo tested historical samples provided in litigation. Test results reveal the presence of asbestos in approximately half of the samples tested. Additionally, fibrous talc was found at varying levels in all samples.(79-83)

Finally, I have reviewed the report of Dr. Michael Crowley that discusses the different chemicals added to the fragrance constituents contained in Johnson's Baby Powder and Shower to Shower products (84)Based on his review, he has concluded that these chemicals may contribute to the potential carcinogenicity of talcum powder products.

Therefore, based on the scientific literature and testing results, it is my opinion that the presence of asbestos, heavy metals, fibrous talc, and fragrances are all biologically plausible explanations for talcum powder products causing ovarian cancer.

Biological Mechanisms

Evidence of Migration of Talcum Powder Products (Talc, Asbestos, Other Minerals) to the Ovary and Fallopian Tubes

Clinical and laboratory studies have shown that talcum powder products can migrate to the ovaries and fallopian tubes. An early surgical study in healthy premenopausal women found that inert particles placed in women's vaginas moved to their fallopian tubes within 30 minutes in two of the three patients studied.(85) Henderson et al. found talc particles in 10 of 13 (75%) of ovarian tumors studied using an extraction-replication technique.(86) The findings were replicated 8 years later, with all surgeons removing the ovaries wearing gloves with no talc, to ensure that surgical contamination was not the cause of the observed talc within ovaries.(87) This replication study found talc in all 9 samples studied—3 normal ovaries, 3 cystic ovaries, and 3 adenocarcinomas.

In another relevant clinical experiment regarding migration, the researchers placed 3 ml of ^{90m}Tc-labelled human albumin microspheres in women's vaginas one day before pelvic surgery.(88) Of the 21 women for whom the materials moved up from the cervical area, ovaries and fallopian tubes could be counted separate from the uterus in 14. Of these 14, 9 showed radioactivity in the fallopian tubes and ovaries, and 5 showed no radioactivity. In a pathological study as part of a case-control study of benign ovarian conditions, ovaries from 24 women were tested for presence of talc and asbestos by both electron microscopy and light microscopy.(64) All tested ovaries were found to have talc present. Only half of the 24 women reported a history of perineal talc exposure, which suggests additional routes of exposure to talc, such as inhaled powder. The presence of talc was not due to surgical gloves as all

surgeons wore talc-free gloves in this study. In another study employing microscopy (Raman), the study authors found talc particles in ovarian tissue samples from a woman with known perineal talc exposure that were not visible with other methods.(89)

Another study demonstrated migration of talc evaluated powder on medical gloves used to perform pelvic examinations (with gloved hand inserted into the vagina).(90) This study detected powder in the peritoneal fluid, fallopian tubes, and ovaries the following day after the pelvic examination in women exposed to powdered gloves but almost none in women exposed to unpowdered gloves. The differences between the two groups were statistically significant.

In 2007, Cramer described the presence of talc particles observed in a pelvic lymph node of a 68 year old woman with stage III serous ovarian carcinoma.(91) The authors used scanning electron microscopy to identify plate-like particulates in the 5-10 µm range within the lymph node, and energy dispersive X-ray spectroscopy revealed a magnesium and silicate signature compatible with talc. The authors also noted that talc could migrate through transport of the lymphatic system.

The results of these studies demonstrate talcum powder products can migrate from the perineal area to the ovaries and fallopian tube through both genital tract migration and inhalation. In my opinion it is biologically plausible that talcum powder products can reach the ovaries via migration from the perineum and via inhalation into the lungs, blood stream, and lymphatic system.

Inflammation in the Causal Pathway between Talcum Powder Product Use and Ovarian Cancer Development

The literature suggests that a likely pathway through which use of talcum powder products increases risk of ovarian cancer is through talc-induced inflammatory response.(92) As described above, it is well supported that talc can migrate through the female genital tract and settle in the area of the ovaries, fallopian tubes, and peritoneum (64, 86-88, 91, 93). Increased blood levels of biomarkers of inflammation have been linked to increased risk for ovarian cancer. A recent meta-analysis of 8 cohort studies found that women with high blood levels of c-reactive protein (a marker of increased systemic inflammation) had almost double the risk of developing ovarian cancer compared with women with low levels.(94)

Further evidence of the inflammation mechanism comes from studies which evaluate anti-inflammatories, like aspirin and NSAIDs, and reduction of risk of ovarian cancer. A pooled analysis of case-control studies published in 2014 showed that long-term daily use of aspirin (which blocks inflammation) decreased risk of ovarian cancer (odds ratio = 0.91; 95% CI = 0.84-0.99) Similar, but not statistically significant, results were shown for use of other nonsteroidal anti-inflammatory medications.(95) A 2018 meta-analysis found an 11% reduced risk of ovarian cancer with aspirin use (relative risk 0.89, 95% CI 0.83-0.95).(96) Aspirin and other nonsteroidal anti-inflammatory medications inhibit the inflammation-mediating enzyme, COX-1(95); COX-1 is frequently overexpressed in ovarian cancer tissue.(97, 98)

Chronic inflammation may result in cell proliferation, inhibition of apoptosis, and secretion of mediators, that may promote tumorigenesis.(92) Factors related to the inflammation of the ovarian surface and tubal epithelium, such as incessant ovulation, endometriosis, and pelvic inflammatory disease, provide further evidence of inflammation and ovarian carcinogenicity. (99-101)

Talc exposure has also been linked to increased inflammation. It can induce granulomas and other inflammatory responses in vivo.(102, 103) Injected into the pleural cavity to treat pneumothorax, talc stimulates an intra-pleural inflammatory reaction that causes pleural fibrosis and scarring, leading to obliteration of the pleural space and prevention of recurrent pneumothoraces.(104) In humans, elevated interleukin 8 (a chemotactic cytokine) occurs after pleural injection of talc.(105) In a study of over 227 patients treated with talc pleurodesis; about half received small particle talc, and half received large-particle talc. Patients who received small particle talc had significantly higher proinflammatory cytokines, particularly interleukin 8, in pleural fluid and serum after talc application.(106) In animal models, injection of talc into the pleura can cause local and systemic inflammatory responses(107) including elevated inflammation-related biomarkers c-reactive protein and interleukin 8(108) as well as VEGF, and TGF-beta.(109) This type of inflammation can induce neoplastic changes.(110)

Additional Evidence of Biological Mechanisms

Exposing human ovarian stromal and epithelial cells to talc resulted in increases reactive oxygen species (oxidative stress), cell proliferation and neoplastic transformation of cells.(110) Similarly, in a recent *in*

vitro study by Fletcher et al., talc was applied in different concentrations, for varying numbers of hours, to epithelial ovarian cancer cell lines and normal ovarian epithelial cells.(111) As early as 24 hours post-treatment, they found increases in mRNA (gene expression) of pro-oxidant enzymes iNOS and MPO in talc-treated epithelial ovarian cancer cells and normal ovarian cells, compared with non-treated controls. Marked decreases in several antioxidant enzymes in talc-treated cells were also seen. This study supports the role of talc in inducing oxidative stress, providing a molecular basis for epidemiologic studies demonstrating an increased risk of ovarian cancer with perineal talcum powder product exposure.(111-113) Another *in vitro* study found that talc induced a biological effect by enhancing CA-125 in ovarian cancer cells and in normal cells.(114)

Talc application to human mesothelial cells in cell culture has also been shown to increase gene expression in 30 genes that are relevant to carcinogenesis, and asbestos application increased gene expression in over 200 genes.(115) In the same study, asbestos application to human ovarian epithelial cells increased gene expression in two genes at 8 hours and 16 genes at 24 hours. Many of the expressed genes are relevant to the carcinogenic process. Results from this experimental study show that talc causes a statistically significant increase in gene expression in mesothelial cells in several genes related to carcinogenesis, including activating transcription factor 3 (ATF3), which controls production of several markers of inflammation.(115)

Asbestos, which has been found in talcum powder products, has been classified by IARC as a known ovarian carcinogen after a systematic review of the epidemiological and biological science.(40) Two meta-analyses and one pooled analysis have addressed the association between asbestos exposure and risk of ovarian cancer.(71-73) The studies of asbestos and ovarian cancer were typically studies of cohorts with high levels of occupational or home asbestos exposure, and comparisons were made to the general population as controls. The most recent meta-analysis found that women exposed to asbestos had a relative risk dying of ovarian cancer of 1.77 (95% CI 1.37-2.28) compared with unexposed populations(71). The other meta-analysis found that women exposed to asbestos had a relative risk of developing or dying of ovarian cancer of 1.75 (95% CI 1.45-2.10) compared with unexposed women(72). An additional four cohort studies (73, 116-119), which were published after the date of the most recent meta-analysis(71),as well as the pooled analysis(73) found similar elevated risks of ovarian cancer in women with asbestos exposure.

IARC also lists mechanisms through which asbestos can cause cancer including: impaired fiber clearance leading to macrophage activation, inflammation, generation of reactive oxygen and nitrogen species, tissue injury, genotoxicity, aneuploidy and polyploidy, epigenetic alteration, activation of signaling pathways, and resistance to apoptosis.(41) Asbestos is another biologically plausible explanation for talcum powder products causing ovarian cancer.

It is my opinion, based on these studies, that talc and asbestos induce inflammation which results in cell proliferation, inhibition of apoptosis, and secretion of mediators, that may promote tumorigenesis. This adds to the weight of evidence and provides a plausible biological explanation for the association between genital talcum powder product use and ovarian cancer.

Another line of experiments in support of the biologically plausible mechanism for talcum powder products causing ovarian cancer were conducted in animals. A study with female rats showed that talc is absorbed through the pleural surface and rapidly disseminated throughout internal organs and lymph nodes.(120) Henderson et al found that talc placed in the uteruses or vaginas of female rats moved to the animals' ovaries by four days post-administration.(121)

In another study, exposure of rat ovaries to talc led to cyst formation and epithelial changes.(122) A methodology study discovered that talc caused superoxide anion generation and release from mouse macrophages.(123)

Animal experiments conducted by the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services are highly relevant to the role of talc in carcinogenesis. An NTP rat study provided important "signal " information of talc toxicity relevant to talc and development of ovarian cancer.(124) In an inhalation study, male and female F344/N rats were exposed to daily talc aerosols of non-asbestiform talc, with appropriate controls. NTP concluded that there was clear evidence of carcinogenic activity of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung, and benign and malignant pheochromocytoma of the adrenal gland. The NTP also concluded that there was some evidence of carcinogenic activity of talc in male F344 /N rats based on an increased incidence of benign and malignant pheochromocytoma of the adrenal gland.

In my opinion, these animal studies further demonstrate that talcum powder products and its attendant inflammation can induce carcinogenesis. This provides further evidence of a biologically plausible mechanism supporting causation of ovarian cancer from the use of talcum powder products.

Summary of Findings: Weight of the Evidence/Bradford Hill Analysis

The summary relative risk estimates from the most recent meta-analyses(34, 35) and the pooled analysis(39) indicate that women who have ever used talcum powder products in the perineal/genital areas (including use of sanitary napkins, diaphragms, underwear, and direct application) have approximately 22-31% increased risk of developing ovarian cancer compared with never-users.

This review of the association between talcum powder products in the perineal/genital area produced several clear findings. Below, they are outlined according to the aspects of causality as described by Bradford Hill.(43) The epidemiologic evidence in total, along with the biological and pathological evidence, fits virtually all of the Bradford Hill aspects for causation, namely: the strength of the association, consistency across populations, specificity, temporality, experiment, biologic gradient (dose-response), plausibility, coherence, and analogy.

Strength of the association and statistical significance: The meta-analyses and pooled analysis showed that risk of ovarian cancer among ever users of talcum powder products is 22-31% higher than in women who never used these products. A total of 28 case-control studies, 3 prospective cohort studies, 2 meta-analyses, and one pooled analysis were reviewed in depth. The meta-analyses found a statistically significant 24 – 25% increased risk of developing serous ovarian cancer—representing 52% of epithelial ovarian cancer cases(125) —in women who had ever used talcum powder products compared with never-users. The pooled analysis, which included data from 5 previously published and 3 unpublished case-control studies, found similar statistically significant increased risks for overall epithelial ovarian cancer and serous ovarian cancer (24% and 20%, respectively). Thus, when combining these studies through meta-analyses, the totality of the evidence shows a statistically significant increased risk of ovarian cancer with use of perineal talcum powder products. Viewed in the context of the high consistency of the study results across time, diverse study populations, and strong study

designs, bias and chance as explanation for the increased risk are unlikely. Further, my confidence in the reliability of the data on magnitude of the risk is enhanced. Therefore, my analysis of these studies strongly supports a causal association and, given the high prevalence of use of talcum powder products in this population, these levels of risk present a clinically significant public health concern. I placed high weight on this aspect of determination of causality.

Consistency of the association: Across the case-control and cohort studies, the association between use of talcum powder products and risk of ovarian cancer was highly consistent. As indicated above, the case-control studies included population-based and hospital-based studies from a diverse geographic area across the U.S., as well as Australia, Canada, the UK, Israel, Greece, and China. Of the 28 studies, 24 found odds ratio greater than 1.1 for ovarian cancer in women who had any perineal exposure to talcum powder products, compared with never users (1-6, 8-11, 13-23, 25-27). Of these 24 odds ratio estimates, 16 were statistically significant (95% confidence intervals excluded 1.0 or p value $\leq$ 0.05). Among the 8 studies which were not statistically significant, 7 had a sample size lower than that estimated to be needed to have power to detect a statistically significant result. Furthermore, the increased risk of ovarian cancer with use of talcum powder products has been seen in various race/ethnic groups as well as in diverse geographic areas around the world. While the cohort studies on average showed more attenuated relative risks of ovarian cancer in relation to use of talcum powder product use, these studies were not well designed to determine true risk for ovarian cancer and perineal talc use. Therefore, their results as a group do not negate the significant case-control study findings and the significant results of the meta-analyses and the pooled analysis.

The most recent and comprehensive meta-analysis by Penninkilampi *et al.*, assessed consistency across the studies included in their analysis by measuring heterogeneity with Cochran's Q statistic, with $P <$ 0.10 indicating heterogeneity.(34) They then quantified the degree of heterogeneity using the I^2 statistic. The I^2 statistic represents the fraction of the total variability across studies that is due to heterogeneity. The authors categorized I^2 values of 25%, 50%, and 75% as corresponding to low, moderate, and high degrees of heterogeneity, respectively, which is typical for meta-analyses.(126) The authors found that there was no heterogeneity in the relative risk estimates for exposure to talcum powder products in the perineal area, or on diaphragms or sanitary napkins. Even though the 95% confidence intervals contained 1.0 in the cohort studies, given the clearly increased relative risk across the case-control

studies, the trend toward increased risk in two of the three cohort studies, and the results from the Penninkilampi et al. meta-analysis, it is my opinion that this did not occur by chance but is, in fact, a true causal relationship.

The consistency across studies, led by many investigators, using different study designs, and in diverse ethnic, racial, and geographic populations over a period of nearly 35 years weighs heavily as to the consistency and reliability of the data in favor of a causal risk. Accordingly, I placed significant weight on this factor in my causation analysis.

Specificity of the association: Use of talcum powder products is strongly associated with epithelial ovarian cancer. Analyses by histologic subtype of epithelial ovarian cancer found that serous ovarian cancer appeared to be most strongly and consistently related to talc exposure, although the pooled case-control project found associations some other subtypes of ovarian cancer. Mucinous cancers have been consistently found to be unrelated to use of these products. Therefore, the specificity aspect is present for epithelial ovarian cancer and certain subtypes. However, because many carcinogens have been shown to cause diverse and nonspecific morbidities, such as smoking, I weighed this aspect moderately in my causal analysis as compared to other Bradford Hill factors.

Temporality: The epidemiologic studies that looked at lifetime talcum powder product use supported that exposure to these products predated the diagnosis of ovarian cancer. I did not find any evidence of 'reverse causation', e.g., using talcum powder products to alleviate symptoms associated with ovarian cancer, nor do any investigators report finding reverse causation. Importantly, symptoms related to ovarian cancer (bloating, increased abdominal size, abdominal pain, pelvic pain, difficulty eating, feeling full quickly)(127) are not vaginal or perineal in origin, and would be unlikely to induce women to increase use of talcum powder products. The finding of temporality is an important component in the causal analysis and, as such, I place great weight in its applicability to the determination of causality.

Biologic gradient/ dose-response: The earlier studies were less likely to address dose-response associations. The larger, and more recent studies, however, collected important data that inform dose-response relationships. Many of the 28 case control studies found evidence of a dose-response effect. Most often, this took the form of lifetime numbers of applications of talcum powder products or years of use. Thus, while there were studies that did not look for or find a dose-response, the body of

literature when taken as a whole does indicate a dose-response effect. Some studies did not gather detailed dose data such as frequency of use or length of use. Others gathered either frequency of the use or duration of use, but not both. As with smoking, ascertainment of frequency x duration of exposure (cumulative exposure) is an optimal metric to determine true dose-response effects. The meta-analyses and the pooled analysis also found evidence of relationships between increasing amount of exposure to talcum powder products in the perineal/genital area (including frequency, years of use, and estimates of lifetime applications) and increased risk of developing epithelial ovarian cancer (i.e., dose-response relationships). Thus, the studies that accurately determined use of talcum powder products revealed evidence of dose-response effects. When present, the finding of a biologic gradient/dose-response is helpful in determining causation. The findings within the study data, particularly meta-analyses and the pooled analysis, thus, supports my causal analysis and I placed significant weight on this factor.

Plausibility: In my consideration of whether talcum powder products can cause cancer, I considered the data for biologically plausible mechanisms by which exposure to talc could result in ovarian cancer. In that regard, I assessed data and determined that talcum powder products can migrate from the perineum through the female genital tract to the ovaries; talcum powder products are found in ovarian and fallopian tube tissues; talcum powder products can induce an inflammatory response; and because of the inflammatory response, malignant transformation can occur. Support for these finding comes from reliable, peer-reviewed scientific literature which indicates that talcum powder products can migrate from the perineum up the genital tract to the fallopian tubes and ovaries and become imbedded in the ovarian tissue. Thus, it is biologically plausible that genital exposure to talcum powder products can result in exposure to the ovaries.

Data also plausibly indicates that inhalation of talcum powder products can result in exposure leading to cancer, including mesothelioma. Studies also show that talcum powder products can be absorbed and transported via the lymphatic system or blood stream. Therefore, inhalation of talcum powder products could result in similar ovarian exposure. Published scientific data shows that talc reaches the ovary and becomes imbedded in the ovarian tissue. There are reliable data to support that talc induces an inflammatory response which mediates oxidative stress, release of cytokines and resulting genotoxicity which can induce malignant transformation. Further, the presence of asbestos and other constituents in

the talcum powder products such as asbestos, heavy metals, and fragrance have been shown to induce cancer by similar mechanisms.

While I have considered the data that do not support the plausibility of talcum powder products' carcinogenicity, otherwise overwhelming and reliable evidence indicates that there are biologically plausible mechanisms by which talcum powder products can induce ovarian carcinogenicity. Talc and its constituents can reach the ovaries, induce an inflammatory response that leads to genotoxicity and to development of ovarian cancer. While this mechanism of carcinogenicity is not proven, it is highly biologically plausible based on the present scientific information and understanding. Therefore, I place significant weight on this aspect of determination of causality.

Coherence: The cause-and-effect interpretation of the data on talcum powder product use and risk of ovarian cancer clearly do not significantly conflict with the known facts about the natural history and biology of the disease. Increased inflammation has been linked to risk of ovarian cancer, and talc and other contents of talcum powder products elicit inflammatory responses within areas of the body in which they have been found (i.e. ovary, peritoneum, lymph nodes, etc.). By analogy, a similar mechanism has been reported by which asbestos causes ovarian cancer. These mechanisms are consistent with one another and the accepted understanding of the role of inflammation in carcinogenesis. While these factors support a causal association and my opinions in this regard, I do not weigh them quite as heavily as the strength and consistency of the association.

Experiment: As discussed above, the evidence from randomized controlled trials can provide strong support to observational evidence. However, here, randomized controlled trials are neither feasible nor ethical, similar to smoking and lung cancer. This is because ovarian cancer is a rare disease and typically takes decades to develop to be clinically diagnosable. In addition, because the effects of genital talcum powder product use could be harmful, it would be unethical to conduct a trial of this type. Furthermore, the studies involving migration of talc, the inflammatory process and its association with carcinogenesis all contribute in a compelling manner to the causal analysis. While there are experimental data supporting causation from cell studies and animal models, given the inability to conduct experimental studies in humans to test effects of talcum powder products on ovarian cancer development, there are no human experimental data. Despite this, data from reliable observational studies as described in this

report strongly support causation. Therefore, I placed slight weight to this aspect of determination of causality.

CONCLUSION

In conclusion, it is my professional opinion, stated to a medical and scientific degree of certainty, that based on the totality of the evidence, which includes epidemiological, biological, pathological and mechanistic data, perineal use of talcum powder products can cause ovarian cancer.

Tables: Epidemiological Studies of Talcum Powder Product Use and Risk of Ovarian Cancer

Table 1: Case-Control Studies

Study	Country	No. Cases	No. Non-cases	Source of participants	Odds Ratio All Ovarian Ca, Any Perineal Talc Use (95% CI)	Odds Ratio Serous Ovarian Ca, Any Perineal Talc Use (95% CI)	Dose-response?
/Schildkraut 2016 (1)	U.S.	584	745	Population	1.44 (1.11-1.86)	1.38 (1.03-1.85)	Yes, OR's: < 3600 apps 1.16 ≥ 3600 apps 1.67 $p_{trend} < 0.01$
Cramer 2016 (2)	U.S.	2041	2100	Population	1.33 (1.16-1.52)	1.42 (a) (1.19-1.69)	Yes > 24 talc-years: OR 1.49 $p_{trend} = 0.02$
Wu 2015 (3)	U.S.	1701	2391	Population	1.46 (1.27-1.69)	Not addressed	Yes, per 5-years talc: OR 1.14 (95% CI 1.09-1.20)
Kurta 2012 (4)	U.S.	902	1802	Population	1.4 (1.16–1.69)	Not addressed	Not addressed
Rosenblatt 2011 (5)	U.S.	812	1313	Population	1.27 (0.97-1.66)	1.47 (borderline) (0.84-2.56) 1.01 (invasive) (0.69-1.47)	No (lifetime number of apps, years of use)
Wu 2009 (6)	U.S.	609	688	Population	1.53 (1.13-2.09)	1.70 (1.27-2.28)	Yes, lifetime apps OR: <=5200: 1.20 >5200 to <=15600: 1.38 >15,600 to <=52000: 1.34 >52000: 1.99

							p_{trend} = 0.0004
Moorman 2009 (7)	U.S.	1114	1086	Population	Whites: 1.04 (0.82-1.33) Blacks: 1.19 (0.68-2.09)	Not addressed	Not addressed
Merritt 2008 (8)	Australia	1576	1509	Population	1.17 (1.01-1.36)	1.21 (1.03-1.44)	Yes, OR: None 1.0 > 0-10 yrs 1.13 > 10-25 yrs 1.08 > 25 yrs 1.29 p_{trend} = 0.02 (similar stat sign trend for serous)
Mills 2004 (9)	U.S.	256	1122	Population	1.37 (1.02-1.85)	1.77 (1.12-2.8)	No (freq X dur), OR Never 1.0 Q1 1.03 Q2 1.81 Q3 1.74 Q4 1.06 p_{trend} = 0.05
Ness 2000 (10)	U.S.	767	1367	Population	1.5 (1.1-2.0)	Not addressed	No (duration only)
Cramer 1999 (11)	U.S.	563	523	Population	1.60 (1.18 - 2.15)	1.38 (borderline) (0.82, 2.31) 1.70 (invasive) (1.22, 2.39)	Yes, lifetime apps when fallopian tubes patent: OR < 3000: 1.54 3000-10,000: 1.72 >10,000: 1.80
Wong 1999 (12)	U.S.	499	755 (non-GYN cancer patients)	Hospital	0.92 (.24-3.62)	1.2 (0.7-2.1)	No (duration only)

Godard 1998 (13)	Canada	170	170	Population	2.49 (0.94-6.58)	Not addressed	Not addressed
Green 1997 (14)	Australia	824	855	Population	1.3 (1.1-1.6)	Not addressed	No (duration only, data not shown)
Cook 1997 (15)	U.S.	313	422	Population	1.5 (1.1-2.3)	1.70 (1.1-2.50)	No (cumulative lifetime days)
Chang 1997 (16)	Canada	450	564	Population	1.42 (1.08-1.86)	1.34 (0.96-1.85)	No (frequency or duration)
Shushan 1996 (17)	Israel	200	408	Population	2.0 (p=0.04)	Not addressed	Not addressed
Cramer 1995 (18)	U.S.	450	454	Population	1.6 (1.2-2.1)	Not addressed	Not addressed
Purdie 1995 (19)	Australia	824	860	Population	1.27 (1.04-1.54)	Not addressed	Not addressed
Tzonou 1993 (28)	Greece	189	200	Hospital	1.05 (0.28-3.98)	Not addressed	Not addressed
Rosenblatt 1992 (20)	U.S.	77	46	Hospital	1.7 (0.7-3.9)	Not addressed	Yes: >= 37.4 years vs. < 37.4 years: OR 2.4
Chen 1992 (21)	China	112	224	Population	3.9 (0.9-10.63)	Not addressed	Not addressed
Harlow 1992 (22)	U.S.	235	239	Population	1.5 (1.0-2.1)	1.4 (.9-2.2)	Yes, lifetime applications, OR: < 1000: 1.3 1000-10,000: 1.5 > 10,000: 1.8 p_{trend} = 0.09
Booth 1989 (23)	U.K.	235	451	Hospital	Daily 1.3 (0.8-1.0) Weekly 2.0 (1.3-3.4)	Not addressed	Yes, RR: Never 1.0 Rarely 0.9 Monthly 0.7 Weekly 2.0 Daily 1.3 p_{trend} = 0.05

Harlow 1989 (24)	U.S.	116 border-line only	158	Population	1.1 (0.7-2.1)	Not addressed	Not addressed
Whittemore 1988 (25)	U.S.	188	539	Hospital + population	1.45 (p=0.06)	Not addressed	1-20 applications/ mo RR 1.27 (0.82-1.96) > 20 apps/mo RR 1.45 (0.94-2.22) No p_{trend} provided
Hartge 1983 (26)	U.S.	135	171	Hospital	2.5 (0.7-10.0)	Not addressed	Not addressed
Cramer 1982 (27)	U.S.	215	215	Population	1.92 (1.27-2.89)	Not addressed	Not addressed

Table 2: Prospective Cohort Studies

Study Year Published	Country	No. Cases	No. Non-cases	Baseline Age	Years of Follow-up	RR All Ovarian Ca, Any Perineal Talc Use (95% CI)	RR Serous Invasive Ovarian Ca, Any Perineal Talc Use	Dose-response
Sister Study Gonzalez, 2016 (30)	U.S.	154	41,500	54.8	Median 6.6 years	0.73 (0.44-1.21)	Not addressed	Not addressed
Women's Health Initiative Houghton, 2014 (29)	U.S.	429	61,147	63.3	Mean 12.4 years	1.06 (0.87-1.28)	1.13 (0.84-1.51)	No (< 9 vs. 10+ years); no frequency data collected
Nurses Health Study Gertig, 2000 (31)	U.S.	307	78,323	36-61 years in 1982 (year of talcum powder product use data collected)	Not provided	1.09 (0.86-1.37) (ever use perineal talc vs. never use)	1.40 (1.02-1.91)	No (only frequency data collected, no duration data)
Nurses Health Study Gates, 2008 (32)	U.S.	210	600	36-61 years in 1982 (year of talcum powder product use data collected)	Not provided	1.24 (0.83-1.83) ($\geq$1/wk vs. < 1/wk)	1.48 (0.82-2.68) ($\geq$1/wk vs. < 1/wk)	Yes: RR's < 1/wk 0.98 1-6/wk 1.01 > 6/wk 1.44
Nurses Health Study Gates, 2010 (33)	U.S.	797	78,323??	6-61 years in 1982 (year of talcum powder product	Not provided	1.06 (0.89-1.28) ($\geq$1/wk vs. < 1/wk)	1.06 (0.84-1.35)	Not addressed

				use data collected)				

Table 3: Meta-analyses

Study	Number of Studies	Number of Cases	Relative Risk All Ovarian Ca, Any Perineal Talc Use (95% CI)	Relative Risk Serous Ovarian Ca, Any Perineal Talc Use (95% CI)	Dose-Response
Penninkilampi 2018 (34)	27	14,311	1.31 (1.24-1.39)	1.32 (1.22-1.43)	Yes: OR 1.32 for < 3600 applications; OR 1.42 for > 3600 applications
Berge 2017 (35)	27	Not provided, should be same as Penninkilami above	1.22 (1.13–1.30)	1.24 (1.15–1.34)	Yes for duration and frequency: 1) RR per 10-year use 1.16 (95% CI 1.07-1.26); 2) RR per weekly use 1.05 (95% CI 1.04-1.07)
Langseth 2008 (36)	20	Not provided	1.35 (1.26-1.46)	Not addressed	Not addressed
Huncharek 2003 (37)	16	5260	1.33 (1.16-1.45)	Not addressed	No summary estimates calculated. Dose response addressed in 9/16 source studies: no dose-response apparent
Cramer 1999 (11)	14	3834	1.4 (1.2-1.5)	Not addressed	Not addressed
Gross 1995 (38)	10 (N=5 studies with adjusted data and limited to	1509	1.29 (1.02-1.63)	Not addressed	Not addressed

	epithelial ovarian cancers)				
Harlow 1992 (22)	6	1106	1.3 (1.1-1.6)	Not addressed	Not addressed

Table 4: Pooled Analysis

	Number of Studies	Number of Cases	Odds Ratio All Ovarian Ca, Any Perineal Talc Use (95% CI)	Odds Ratio Serous Ovarian Ca, Any Perineal Talc Use (95% CI)	Dose-Response All Ovarian Cancer
Terry 2013 (39)	8	8,525	1.24 (1.15–1.33)	1.24 (invasive) (1.13–1.35)	Yes. OR (95% CI) by quartiles of lifetime applications vs. never use, non-mucinous cases only: Q1 1.18 (1.02-1.36) Q2 1.22 (1.06-1.41) Q3 1.22 (1.06-1.40) Q4 1.37 (1.19-1.58)

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EXHIBIT A

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M.D., 6/89, New York Medical College, Valhalla, NY
Ph.D. in Epidemiology, 12/82, University of Washington, Seattle, WA
M.A. in Medical Sociology, 6/76, State University of New York at Buffalo,
B.A. in Sociology, 1/74, Boston University, Boston, MA

PROFESSIONAL POSITIONS

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA
Director, FHCRC Prevention Center (2002 - 2012)
Full Member (2001 - present)
Associate Member (1997 – 2001)
Assistant Member (1996 - 1997)
Senior Staff Scientist, Associate in (1983 – 1985; 1992 - 1996)
Department of Epidemiology, University of Washington School of Public Health, Seattle, WA
Research Professor (2003 -)
Research Associate Professor (1999 – 2003)
Research Assistant Professor (1996 - 1999)
Clinical Instructor (1992 - 1996)
Department of Medicine, Division of Geriatrics
Adjunct Research Professor (2003 -)
Adjunct Research Associate Professor (1999 - 2003)
Department of Medicine, Division of General Internal Medicine
Clinical Instructor (1992 – 1996)
Clinical Nutrition Research Unit, University of Washington, Seattle WA
Affiliate Investigator (1996 – present)
Harborview Medical Center, Adult Medicine Clinic, Seattle, WA
Attending Physician (1992 - 1995)
University of Washington, Women's Primary Care Clinic, Seattle, WA
Attending Physician (1996)

HONORS and TRAINEESHIPS

- American College of Sports Medicine Citation Award, 2012
- McDougall Mentoring Award, Fred Hutchinson Cancer Research Center, 2011
- Komen for the Cure Scientific Advisory Council/Komen Scholars, 2010-2012
- University of Washington Roger E. Moe Award for Translational Research 2009
- The Joan P. Liman MD Award, Recipient, New York Medical College, 1989
- National Institute for Dental Research, Fellowship Award in Behavioral Dental Research, 1983
- National Cancer Institute Traineeship, 1980-1982

- University of Washington Public Health Traineeship, 1978-1979

PROFESSIONAL ACTIVITIES
Committee Memberships and Academic Consulting

- 2018 U.S. Dept. Health and Human Services Physical Activity Guidelines Advisory Committee, 2016-2018
- Member, External Advisory Board, Pennington Biomedical Research Center, Louisiana, 2018
- Reviewer, NIEHS Sisters Study, 2018
- Patient-Centered Outcomes Research Institute Advisory Panel on Clinical Trials, 2014-2016
- University of Alabama, Center for Exercise Medicine External Advisory Committee, 2016
- Program Committee Member, American Institute for Cancer Research 2016 Conference on Nutrition, Physical Activity, Obesity and Cancer
- Consortium Member: NCI Randomized Controlled Trials of Lifestyle Weight Loss Interventions for Genome-Wide Association Studies, 2016-
- AACR Cancer Prevention Committee, 2010-
- World Cancer Research Fund (WCRF) Continuous Update Project Panel, 2010-
- 2008 U.S. Dept. Health and Human Services Physical Activity Guidelines Advisory Committee, 2007- 2008 (Chair, Cancer Working Group)
- Cancer Prevention Research Institute of Texas, Prevention Review Committee, 2009-2015
- Chair, Transdisciplinary Research on Energetics and Cancer (TREC) Steering Committee 2006-7
- Chair, Cancer Interest group, the Obesity Society, 2006-7
- Steering Committee for International Position Paper and Consensus Conference on Women's Health and the Menopause, NHLBI-Lorenzi Foundation sponsors, 1998 – 2002
- International Advisory Board to the 4th International Symposium on Women's Health and Menopause, 2000 – 2001 and 2004
- Professional Advisory Committee, Breastcancer.org, 2003 –
- Women's Health Research Coalition, 2002
- Women's Health Initiative Committee Membership: Morbidity and Mortality (Co-Chair); Performance Monitoring Outcomes Committee (Chair); Coordinating Center Outcomes Scientific Committee (Chair); Coordinating Center Representative to WHI Program Advisory Committee, 1994-1995; Genetics Working Group; Cancer Biomarkers Working Group
- Consultant, *Moving Forward Study*, University of Illinois, Chicago (PI, Melinda Stolley), 2013-
- Consultant, *The Energy Balance and Breast Cancer Aspects studies: EBBA-I and EBBA-II*, Oslo University Hospital, Oslo, Norway (PI, Inger Thune), 2013-
- American Institute of Cancer Research Meeting Program Committee member, 2010, 2016
- Cancer Prevention Expert Panel, Pennington Biomedical Research Center (Baton Rouge, LA), 2010
- External Advisory Committee, Cooper Clinic, Dallas, Tx, April 2006
- Steering Committee, LISA Trial of Weight Loss for Breast Cancer Patients, Novartis Canada 2005 – 2007
- Chair, Breast Clinical Endpoints Committee, DANCE trial of testosterone patch safety, Proctor & Gamble, 2006-7
- External Reviewer for NCI Nutritional Epidemiology Program, 2005, 2013
- Data and Safety Monitoring Board, "Project Alive", Kaiser Oakland (B. Sternfeld, PI)
- Member, NCI Transdisciplinary Research Working Group, co-Chair section on Lifestyle, 2006
- Panels for American Cancer Society Guidelines on *Diet, Nutrition and Cancer Prevention* and Guidelines for Cancer Patients and Survivors (2001, 2003, 2005)
- Working Group for International Agency for Research on Cancer Handbook of Cancer Prevention: Volume 6 – Weight control and physical activity, 2000 – 2001
- Advisory Board for the Tomorrow Study (Alberta, Canada, Cancer Cohort Study), 1999 - 2001
- Advisor to The effects of weight loss and exercise on biomarkers of breast cancer risk- a randomized pilot trial (M. Harvie, A. Howell, Manchester, England)
- Participant, "Workshop on Physical Activity and Breast Cancer", National Action Plan on Breast Cancer, Nov. 1997

- Invitee, "Beyond Hunt Valley: Research on Women's Health for the 21st Century", Nov. 1997
- Participant, "Breast Cancer in Minorities", National Action Plan on Breast Cancer, March 1999
- 2005 ASPO Annual Meeting Program Committee
- Member, Steering Committee for International Position Paper and Consensus Conference on Women's Health and the Menopause, NHLBI-Lorenzi Foundation sponsors, 1998

Editorial Boards

- Cancer Prevention Research, 2008 - 2014
- Journal of Women's Health, 1998 –
- Medscape Women's Health and Ob/Gyn & Women's Health, 2001 – 2002

Grant Reviewing

- Chair, Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program - Prevention, January 2017
- Member, Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program - Prevention, January 2018
- Florida Department of Health Research Program Peer Review, 2017
- Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program - Epidemiology, February, 2016
- NCI Omnibus: Biomarkers R03 & R21 SEP-12 Review Committee 2015
- NCI Omnibus: Cancer Management & Behavior 2014
- MD Anderson NCI CCSG Review 2013
- Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program Breakthrough Award, Epidemiology/Prevention 2013
- Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program Training-Epidemiology - Prevention (2 cycles) 2013
- NIH Special Emphasis Panel Member September 2012
- NIH PRDP Study Section Member 2008-2012 (ad hoc 2006-2008)
- Susan G. Komen for the Cure 2009 - 2013
- Cancer Prevention & Research Institute of Texas 2009 – 2015
- Qatar National Priorities Research Program 2010-2013
- Catalan TV3 Marató Call 2005, 2013
- San Diego State/UC San Diego Pilot Grant Reviewer 2012
- FHCRC and UW Pilot Grant Reviews yearly
- NCI Cancer Centers Review Group Ad Hoc Member May 2007
- Pennsylvania Interim Performance Review 2007, 2008, 2010, 2012
- Marsha Rivkin Center for Ovarian Cancer Research Grants 2012
- Memorial Sloan Kettering Cancer Center NCI CCSG Review 2007
- Department of Defense Breast Cancer Program Predoctoral Fellowship Grants, 2006
- Chair, NIH Special Study Section "Mechanisms of Physical Activity Behavior Change" 3/04
- NIH EDC-2 Special Study Section, Sept. 9-10, 1997
- Alberta Cancer Board Grants, 1998-2002 and other Canadian agencies, and for Spanish and Italian Foundations
- NCI Administrative Supplements for Disseminating Evidence-based Research Products 8/04
- Member, ACSM Research Review Committee 2004 – 2006

Journal Reviewing

- JAMA, Archives of Internal Medicine, American Journal of Epidemiology, Journal of the National Cancer Institute, Annals of Internal Medicine, European Journal of Cancer, British Journal of Cancer, Cancer Causes & Control, Cancer Epidemiology Biomarkers & Prevention, Annals of Epidemiology, Epidemiology, and Nutrition

College Fellowship and Membership
- The Obesity Society (Fellow 2003 -)
- American College of Sports Medicine (Fellow 2003 -)
- American College of Epidemiology (Fellow 1999 -)

Professional Licenses and Certification
- Board Certified, American Board of Internal Medicine, 1992
- Physician & Surgeon License, State of Washington, 7/21/91-2/18/18
- DEA License, Expires 2017, Schedules 2, 2N, 3, 3N, 4, 5

LEADERSHIP
- Director, FHCRC Prevention Center, 2002-2012
- Chair, TREC Steering Committee 2006-7
- Chair, Cancer Interest Group, Obesity Society 2007-8
- Chair, Cancer Subcommittee, DHHS Physical Activity Guidelines Advisory Committee 2016-18
- Member, Leadership Group, DHHS Physical Activity Guidelines Advisory Committee 2016-18
- Chair, Cancer Working Group, DHHS Physical Activity Guidelines Advisory Committee 2007-8
- Chair, Section on Mechanisms, IARC Handbook of Cancer Prevention 2002: Physical Activity and Weight Control, 2000-1
- Organized and Chaired Symposium on Physical Activity and Cancer, American College of Sports Medicine, St. Louis, June 2002

REFEREED PUBLICATIONS
(** refers to student papers under my supervision; ^ denotes papers from studies on which I was PI)

1983
1. Shy K, **McTiernan A**, Daling J, and Weiss N: Oral contraceptive use and the occurrence of pituitary prolactinoma. Journal of the American Medical Association 249:2204-2207, 1983.

1984
2. ^**McTiernan A**, Weiss N, and Daling J: Incidence of thyroid carcinoma in women in relation to reproductive and hormonal factors. American Journal of Epidemiology 120:423-435, 1984.
3. ^**McTiernan A**, Weiss N, and Daling J: Incidence of thyroid carcinoma in women in relation to radiation exposure and history of thyroid disease. Journal of the National Cancer Institute 73:575-581, 1984.

1985
4. **McTiernan A**, Chu J, and Thomas D: Cancer in whites in the Pacific Basin. In Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin. National Cancer Institute Monograph 69:65-72, 1985.

1986
5. ^**McTiernan A**, Weiss N, and Daling J: Bias resulting from using the card-back system to contact patients in epidemiologic studies. American Journal of Public Health 76:71-73, 1986.
6. **McTiernan A**, Whitehead A, Thomas D, and Noonan E: Efficient selection of controls for multi-centered collaborative studies of rare diseases. American Journal of Epidemiology 123:901-904, 1986.
7. **McTiernan A**, Thomas D, Johnson L, and Roseman D: Risk factors for estrogen receptor-rich and estrogen receptor-poor breast cancers. Journal of the National Cancer Institute 77:849-854, 1986.
8. **McTiernan A** and Thomas D: Evidence for a protective effect of long-term lactation on risk of breast cancer: results from a case-control study. American Journal of Epidemiology 124:353-358, 1986.
9. ^Mueller B, **McTiernan A**, and Daling J: Level of response in epidemiologic studies using the card-back system to contact patients. American Journal of Public Health 76:1331-1332, 1986.

1987

10. ^**McTiernan A**, Weiss N, and Daling J: Incidence of thyroid cancer in women in relation to known or suspected risk factors for breast cancer. Cancer Research 47:292-295, 1987.

1991

11. Rosenblatt KA, Thomas DB, **McTiernan A**, et al: Breast cancer in men: aspects of familial aggregation. Journal of the National Cancer Institute 83:849-54, 1991.
12. Demers PA, Thomas DB, Rosenblatt KA, **McTiernan A**, et al: Occupational exposure to electromagnetic fields and breast cancer in men. American Journal of Epidemiology 134:340-47, 1991.

1992

13. Thomas DB, Jiminez LM, **McTiernan A**, et al: Breast cancer in men: risk factors with hormonal implications. American Journal of Epidemiology 135:734-48, 1992.

1993

14. Stalsberg H, Thomas DB, Rosenblatt KA, Jiminez LM, **McTiernan A**, et al: Histologic types and hormone receptors in breast cancer in men--a population-based study in 282 North American men. Cancer Causes and Control 4:143-51, 1993.

1994

15. Thomas DB, Rosenblatt K, Jiminez LM, **McTiernan A**, et al: Ionizing radiation and breast cancer in men. Cancer Causes and Control 5:9-14, 1994.

1995

16. Bowen D, Green P, Kestin M, **McTiernan A**, Carroll D: Effects of decreasing dietary fat on psychological well-being. Cancer Epidemiology, Biomarkers, and Prevention 4:555-59, 1995.
17. **McTiernan A**, Rossouw J, Manson J, et al: Informed consent in the Women's Health Initiative. Journal of Women's Health 5:519-529, 1995.

1996

18. Prentice R, Rossouw JR, Johnson, SR, Freedman LS, **McTiernan A**. The role of randomized controlled trial in assessing the benefits and risks of long-term hormone replacement therapy: example of the Women's Health Initiative. Menopause, 1996;3:71-76.
19. **McTiernan A**, Stanford JL, Weiss NS, Daling JR, Voigt LF: Occurrence of breast cancer in relation to recreational exercise in women age 50-64 years. Epidemiology 1996;7:598-604.

1997

20. Burke W, Peterson G, Lynch P, Botkin J, Daly M, Garber J, Kahn MJE, **McTiernan A**, Offitt K, Thomson E, Varricchio C, for the Cancer Genetics Studies Consortium. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. 1. Hereditary nonpolyposis colon cancer. JAMA 1997;277:915-919.
21. Burke W, Daly M, Garber J, Botkin J, Kahn MJE, Lynch P, **McTiernan A**, Offitt K, Perlman J, Petersen G, Thomson E, Varricchio C, for the Cancer Genetics Studies Consortium. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. 2. BRCA1 and BRCA2. JAMA 1997;277:997-1003.
22. **McTiernan A**, Gilligan M, Redmond C: Assessing individual risk for breast cancer: risky business. J Clinical Epidemiology 1997;50:547-556.

1998

23. Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical Trial and Observational Study. Controlled Clinical Trials 1998;19:61-109.
24. **McTiernan A**, Stanford J, Daling J, Voigt L: Prevalence and correlates of physical activity in women aged 50-64 years. Menopause 1998;5:95-101.
25. ^**McTiernan A**, Kumai C, Bean D, Hastings R, Schwartz R, Ulrich N, Gralow J, Potter J. Anthropometric and hormone effects of an 8-week exercise-diet intervention in breast cancer patients: results of a feasibility pilot study. Cancer Epidemiology Biomarkers Prevention 1998;7:477-81.
26. Hoffman-Goetz L, Apter D, Demark-Wahnefried W, Goran M, **McTiernan A**, Reichman M. Mechanisms for an association between physical activity and breast cancer. Cancer (supplement) 1998;83:621-628.
27. **McTiernan A**, Ulrich N, Slate S, Potter J. Physical activity and cancer etiology: associations and mechanisms. Cancer Causes and Control 1998;9(5)487-509.

1999

28. Cheblowski RT, **McTiernan A.** Elements of informed consent for Hormone Replacement Therapy in patients with diagnosed breast cancer. Journal of Clinical Oncology 1999;17(1):130-42.
29. ^Negri E, Ron E, Franceschi S, DalMaso L, Mark SD, Preston-Martin S, **McTiernan A**, et al. A pooled analysis of thyroid cancer case-control studies: Methods. Cancer Causes and Controls 1999:10:131-142.
30. ^Negri E, DalMaso L, Ron E, LaVecchia C, Mark SD, Preston-Martin S, **McTiernan A**, et al. Menstrual and reproductive factors and thyroid cancer. Cancer Causes and Controls 1999:10:143-155.
31. ^LaVecchia C, Ron E, Franceschi S, DalMaso L, Mark SD, Chatenoud L, Braga C, Preston-Martin S, **McTiernan A**. Oral contraceptives, menopausal replacement treatment and other female hormones and thyroid cancer. Cancer Causes and Controls 1999:10:157-166.
32. Durfy S, Bowen D, Burke W, **McTiernan A,** et al. Attitudes and interest in genetic testing for breast and ovarian cancer susceptibility in diverse groups of women in Western Washington. Cancer Epidemiology Biomarkers and Prevention 1999:8;369-376.
33. ^**McTiernan A**, Ulrich CM, Yancey D, Slate S, Nakamura H, Oestreicher N, Bowen D, Yasui Y, Potter J, and Schwartz R. The Physical Activity for Total Health (PATH) Study: rationale and design. Medicine and Science in Sports and Exercise 1999;31:1307-1312.
34. **McTiernan A**, Potter J, Bowen D, Schwartz R. Exercise clinical trials in cancer prevention research: a call to action. Cancer Epidemiology Biomarkers and Prevention 1999; 8:201-207.
35. Bowen D, **McTiernan A**, Burke W, Powers D, Pruski J, Durfy S, Gralow J, Malone K. Participation in breast cancer risk counseling among women with a family history. Cancer Epidemiology Biomarkers and Prevention 1999; 8:581-586.
36. Rosenblatt KA, Thomas DB, Jimeneq LM, Fish B, **McTiernan A**, et al. Diet and breast cancer in men. Cancer Causes and Control 1999;10:107-113.
37. ^Franceschi S, Preston-Martin S, DalMaso L, Negri E, LaVecchia C, **McTiernan A**, et al. A pooled analysis of thyroid cancer case-control studies. IV. Benign thyroid diseases. Cancer Causes and Control 1999;10:583-595.
38. ^LaVecchia C, Ron E, Franceschi S, DalMaso L, Mark SD, Chatenoud L, Braga C, Preston-Martin S, **McTiernan A**. A pooled analysis of thyroid cancer studies. Anthropometric factors. Cancer Causes and Control 1999;10:583-595.

2000

39. Burke W, Culver JB, Bowen D, Lowry D, Durfy S, **McTiernan A**, Anderson, MR. Genetic counseling for women with an intermediate family history of breast cancer. American Journal of Medical Genetics 2000;90(5):361-8.
40. **McTiernan A.** The associations of energy balance and body mass index with breast cancer risk in United States women from diverse racial and ethnic backgrounds. Cancer 2000;88:1248-1255.
41. Bowen DJ, **McTiernan A**, , Rosenberg E, Powers P, Feng Z: Recruiting women into a smoking cessation program to control weight: who might quit? Women and Health 2000;31(4):41-58.
42. Wingo PA, Calle EE, **McTiernan A**. How does breast cancer mortality compare with other cancers and cardiovascular disease at different ages in U.S. women? Journal of Women's Health 2000;9:999-1006.
43. **McTiernan A.** Physical Activity and the Prevention of Breast Cancer. Medscape. Invited as Expert Opinion. October 2000; 5(5). Available at http://www.medscape.com/Medscape/WomensHealth/ journal/2000/v05.n05/wh7419.mcti/wh7419.mcti-01.html

2001

44. ******Young SYN, Gunzenhauser JD, Malone KE, **McTiernan A.** The relationship between body mass index and asthma in the military population of the northwestern United States. Archives Internal Medicine 2001;161:1605-1611.
45. Davidoff R, **McTiernan A**, Constantine G, Davis KD, Balady GJ, Mendes LA, Rudolph RE, Bowen, DJ. Echocardiographic evaluation of women previously treated with fenfluramine: Long-term follow-up of a randomized, double-blind, placebo-controlled trial. Archives of Internal Medicine. 2001;161:1429-1436.
46. Marrett L, Theis B, Ashbury FD, and an Expert Panel. Workshop report: physical activity and cancer prevention. (member of the expert panel). Chronic Diseases in Canada 2001;21:143-149.
47. La Vecchia C, Brinton L, **McTiernan A**. Menopause, hormone replacement therapy and cancer. Maturitas 2001; 39: 97-115.
48. **McTiernan A,** Burke W, Bars J, et al. Comparison of two breast cancer risk estimates in women with a family history of breast cancer. Cancer Epidemiology Biomarkers and Prevention 2001;10: 333-338.

49. ^Bosetti C, Kolonel L, Negri E, Ron E, Franceschi S, Dal Maso L, Galanti MR, Mark SD, Preston-Martin S, **McTiernan A**, Land C, Mabuchi K, Jin F, Wingren G, Hallquist H, Glattre E, Lund E, Levi F, Linos D, La Vecchia C. A pooled analysis of case-control studies of thyroid cancer: fish and shellfish consumption. Cancer Causes and Control 2001;12:375-382.
50. Shors AR, Solomon C, **McTiernan A**, White E. Melanoma risk in relation to height, weight, and exercise (United States) Cancer Causes and Control 2001; 12(7):599-606. Cancer Causes Control. 2001 Sep;12(7):599-606.
51. Tavani A, La Vecchia C, Brinton LA, **McTiernan A.** Hormone replacement therapy and risk of endometrial cancer. Tumori. 2001 Sep-Oct;87(5):S20-1.
52. LaVecchia C, Brinton LA, **McTiernan A**. Hormone replacement therapy and breast cancer risk: epidemiology. Journal fur Menopause 2001;8:5-7.
53. Friedenreich C, Marrett LD, Members of the Canadian Breast Cancer Initiative Working Group on Primary Prevention of Breast Cancer and an Expert Panel. Workshop report: identification of research needs in breast cancer etiology. Chronic Diseases in Canada 2001;22:41-49 (member of the Expert Panel).

2002

54. ^**Irwin ML, **McTiernan A**. Exercise effect on body weight in postmenopausal women: the Physical Activity for Total Health Study. In RA Lobo, PG Crosignani, R Paoletti, F Bruschi (eds). Women's Health and Menopause: New Strategies – Improved Quality of Life, Dordrecht, Kluwer Academic Pub. 2002, pp. 345-352.
55. Chlebowski RT, Aiello E, **McTiernan A.** Weight loss in breast cancer patient management. J. Clinical Oncology 2002;20(4):1128-1143.
56. ^**Slate S, Yasui Y, Ulrich C, **McTiernan A**. Mailing strategies and recruitment into an intervention trial of the exercise effect on breast cancer biomarkers. Cancer Epidemiology Biomarkers and Prevention 2002; 11: 73-77.
57. Hendrix S, Clark A, Nygaard I, Aragaki A, Barnabei V, **McTiernan A**. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J. Obstet Gynecol 2002 Jun;186(6):1160-6.
58. Wenger NK, Paoletti R, Lenfant CJM, Pinn VW, Barrett-Connor E, Birkhauser MH, Brinton LA, Collins A, Collins P, Crosignani PG, Dennerstein L, Ettinger B, Gustafson JA, Guthrie J, Henderson VW, Hendrix S, Klein BEK, LaVecchia C, Lindsay R, Maggi A, McGowan JA, **McTiernan A,** Nilsson S, Redford M, Resnick SM, Rossouw JE, Santoro N, Sherman SS. Executive summary. In International Position Paper on Women's Health and Menopause: a Comprehensive Approach. Wenger NK, Paoletti R, Lenfant CJM, Pinn VW (eds). NIH Publication No. 02-3284. 2002, pp. 1-22.
59. LaVecchia C, Brinton L, **McTiernan, A** Hormone replacement therapy, related therapies, and cancer. In International Position Paper on Women's Health and Menopause: a Comprehensive Approach. Wenger NK, Paoletti R, Lenfant CJM, Pinn VW (eds). NIH Publication No. 02-3284. 2002, pp.223-250.
60. Barrett-Connor E, Hendrix S, Ettinger B, Wenger NK, Paoletti R, Lenfant CJM, Pinn VW, Birkhauser MH, Brinton LA, Collins A, Collins P, Crosignani PG, Dennerstein L, Gustafson JA, Guthrie J, Henderson VW, Klein BEK, LaVecchia C, Lindsay R, Maggi A, McGowan JA, **McTiernan A,** Nilsson S, Redford M, Resnick SM, Rossouw JE, Santoro N, Sherman SS. Best clinical practices: a comprehensive approach. In International Position Paper on Women's Health and Menopause: a Comprehensive Appoach. Wenger NK, Paoletti R, Lenfant CJM, Pinn VW (eds). NIH Publication No. 02-3284. 2002, pp. 271-288.
61. Byers T, Thun M, **McTiernan A**, Doyle C, et al. American Cancer Society Guidelines for Nutrition and Physical Activity and Prevention of Cancer. CA: Cancer J Clin 2002;52:92-119.
62. Morimoto L, White E, Zhao C, Chlebowski R, Hays J, Kuller L, Lopez AM, Manson J, Margolis K, Muti P, Stefanick M, **McTiernan A**. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative. Cancer Causes and Control. 2002;13:741-751.
63. ^Bossetti C, Kolonel L, Negri E, Ron E, Franceschi S, Dal Maso L, Galanti MR, Mark SD, Preston-Martin S, **McTiernan A**, Land C, Mabuchi K, Jin F, Wingren G, Hallquist H, Glattre E, Lund E, Levi F, Linos D, La Vecchia C. A pooled analysis of case-control studies of thyroid cancer. VII. Cruciferous and other vegetables. Cancer Causes and Control 2002;13:765-775.
64. LaVecchia C, Brinton LA, **McTiernan A.** Cancer risk in postmenopausal women. Bailliere's Best Practice and Research - Clinical Obstetrics & Gynaecology 2002 Jun;16(3):293-307.
65. Andersen R, Bowen D, Yasui Y, **McTiernan A**. Awareness and concern about ovarian cancer among women at risk due to a family history of breast or ovarian cancer. Clinical Journal of Women's Health 2002;2:5-12. (also reprinted in Am J Obstet Gynecol. 2003 Oct;189(4 Suppl):S42-7.)

66. Bowen D, Burke W, Yasui Y, **McTiernan A**, McLaren D. Effects of risk counseling on interest in genetic testing in lower risk women. Genetics in Medicine 2002; 4:359-365.
67. Evenson K, Wilxox S, Pettinger M, Brunner R, King AC, **McTiernan A**. Vigorous leisure activity through women's adult life: The Women's Health Initiative Observational Cohort Study. American Journal of Epidemiology 2002;156:945-953.

2003

68. Bowen D, Powers D, Anderson R, Burke W, **McTiernan A,** Durfy S, Helmes A. Predicting breast cancer screening with emotion and cognition. Journal of Social and Clinical Psychology 2003;22(2):213-232.
69. ^**Irwin M, Yasui Y, Ulrich CM, Bowen D, Rudolph RE, Schwartz RS, Yukawa M, Aiello E, Potter JD, **McTiernan A**. Effect of exercise on total and intra-abdominal body fat in postmenopausal women: a randomized controlled trial. JAMA 2003;289: 323-330.
70. ^**McTiernan A**, Rajan KB, Tworoger S, Irwin M, Bernstein L, Baumgartner R, Gilliland F, Stanczyk F, Yasui Y, Ballard-Barbash R. Adiposity and sex hormones in postmenopausal breast cancer survivors. Journal of Clinical Oncology 2003;21(10):1961-1966.
71. Curb D, **McTiernan A**, Heckbert S, Kooperberg C, Stanford J, Nevitt M, Johnson K, Proulx-Burns L, Pastore L, Criqui M, Dougherty S. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. Annals of Epidemiology 2003;13(9, Suppl 1):S122-S128.
72. ^**Irwin M, Crumley D, **McTiernan A**, Bernstein L, Baumgartner R, Gilliland F, Kriska A, Ballard-Barbash R. Physical activity levels before and after a diagnosis of breast cancer: The Health, Eating, Activity, and Lifestyle (HEAL) Study. Cancer 2003;97:1746-57.
73. Mitchell BL, Ulrich CM, **McTiernan A**. Vitamin supplementation and immune function: can the elderly benefit? (review) Nutrition Research 2003; 23:1117-39
74. Chlebowski R, Cyr M, Gass M, Gilligan M, Hendrix S, Handek CJ, Lane D, Langer RD, Petrovich H, Stefanick M, Thomson C, **McTiernan A.** Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003;289: 3243-53.
75. **McTiernan A.** Intervention studies in exercise and cancer prevention. (American College of Sports Medicine Symposium paper) Medicine and Science in Sports and Exercise. 2003;35(11):1841-1845.
76. ^**Tworoger S, Yasui Y, Ulrich CM, Vitiello M, Bowen D, Irwin M, Aiello EJ, Schwartz RS, Potter J, **McTiernan A.** Effect of a yearlong moderate to vigorous intensity exercise or low intensity stretching intervention on self-reported sleep quality measures in postmenopausal women. Sleep 2003;26(7): 830-6.
77. **McTiernan A**. Behavioral risk factors in breast cancer: can risk be modified? The Oncologist. 2003;8(4):326-34.
78. Harris RE, Chlebowski RT, Jackson RD, Frid DJ, Ascenseo JL, Anderson G, Loar A, Rodabough RJ, White E, **McTiernan A**; Women's Health Initiative. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. Cancer Res. 2003 Sep 15;63(18):6096-101.
79. Brown JK, Byers T, Doyle C, Courneya KS, Demark-Wahnefried W, Kushi LH, **McTiernan A,** et al, Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin. 2003 Sep-Oct;53(5):268-91.
80. **McTiernan A**, Kooperberg C, White E, Wilcox S, Coates R, Adams-Campbell L, Woods N, Ockene J. Recreational physical activity and the risk of breast cancer in postmenopausal women. The Women's Health Initiative Cohort Study. JAMA 2003; 290: 1331-1336.
81. ^Mack WJ, Preston-Martin S, Dal Maso L, Galanti R, Xiang M, Franceschi S, A Hallquist A, Jin F, Kolonel L, La Vecchia C, Levi F, Linos A, Lund E, **McTiernan A**, Mabuchi K, Negri E, Wingren G, Ron E. A pooled analysis of case–control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea. Cancer Causes and Control 2003;14 (8): 773-785.

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2. **McTiernan A**, Gralow J, Talbott L. *Breast Fitness: An Optimal Exercise and Health Plan for Reducing Your Risk of Breast Cancer.* St. Martin's Press, New York. October 2000 (hardcover), October 2001 (softcover)
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MANUSCRIPTS SUBMITTED FOR PUBLICATION

1. Frydenberg H, Ursin G, Iversen A, Fagerland MW, Ellison PT, Wist EA, Egeland T, Wilsgaard T, **McTiernan A**, Furberg A-S, Thune I. High-density lipoprotein-cholesterol (HDL-C), daily estradiol and progesterone and mammographic density in premenopausal women. Submitted to The Breast 2015
2. Lofterød T, Frydenberg H, Eggen AE, **McTiernan A**, Mortensen ES, Wist EA, Akslen LA, Reitan JB, Wilsgaard T, Thune I. Triglycerides and weight change throughout life influence breast cancer development. The EBBA Life study. Submitted to Cancer Causes & Control 2016.
3. Mason C, deDieu Tapsoba J, Duggan C, Wang CY, Alfano CM, **McTiernan A**. Disordered eating behaviors and weight loss outcomes in a 12-month randomized trial of diet and/or exercise intervention in postmenopausal women. Submitted to American Journal of Clinical Nutrition 2018.
4. Chan DS, Abar L, Cariolou M, Nanu N, Greenwood DC, Bandura EV, **McTiernan A**, Norat T. World Cancer Research Fund International – Continuous Update Project: systematic literature review and meta-analysis of cohort studies on physical activity, adiposity, and weight change and breast cancer risk. Submitted to British Medical Journal. 2018

INVITED SCIENTIFIC PRESENTATIONS (does not include conference abstracts)

1. "Women's Health and the Women's Health Initiative." Fred Hutchinson Cancer Research Center, WHI Clinical Center Staff Trainings, 1993-1997.
2. "The Women's Health Initiative: An Overview." University of Washington, Department of Epidemiology Seminars, February 8, 1994.
3. "Risk Assessment for Breast Cancer." University of Washington, Department of Surgery Breast Cancer Conference, April 26, 1994.
4. “Risk Assessment for Breast Cancer.” Breast Cancer in Young Women, University of Washington Continuing Education Conference, August 6, 1994.
5. “Assessing Individual Risk for Breast Cancer.” Cancer in Lesbians Symposium, Fred Hutchinson Cancer Research Center, December 2, 1994.
6. “Breast Cancer in High Risk Populations: Women’s Health Initiative.” Fred Hutchinson Cancer Research Center Scientific Retreat, December 7, 1994.
7. “The Women’s Health Initiative.” Invited presentation at American Society for Preventive Oncology, Women’s Cancers Study Group Meeting, March 11, 1995.
8. “Prevention in Practice and Trials.” Current Concepts in the Early Detection of Breast Cancer, Multicare, Madigan Army Medical Center, and American Cancer Society 3rd Annual Oncology Conference, April 11, 1995.
9. “Exercise and Breast Cancer.” Beating Breast Cancer in the ‘90’s: What Everyone Needs to Know about Breast Cancer, University of Washington/Fred Hutchinson Cancer Research Center, April 23, 1996.
10. “Women’s Health Initiative.” Women’s Health Grand Rounds, University of Washington Medical Center-Roosevelt, January 6, 1996.
11. “Exercise and Cancer.” Interdisciplinary Cancer Course, Fred Hutchinson Cancer Research Center, March 26, 1997.
12. “Exercise and Breast Cancer.” Nutrition Seminar, Department of Nutrition, University of Washington School of Public Health, April 10, 1997.
13. Panel Discussant, “Epidemiologic Issues”, NAPBC Workshop on Physical Activity and Breast Cancer, Nov 13-14, 1997.
14. “Diet and Exercise” Breast Cancer Forum: Clinical Implications of Current Research, FHCRC, October 7, 1998.
15. “Exercise and Breast Cancer” American College of Sports Medicine, Seattle, WA, June 2, 1999.
16. “Physical Activity and Reproductive Hormones” Cooper Institute Conference on Physical Activity and Cancer, Dallas, Texas, November 5-7, 2000
17. “Weight Matters in Breast Cancer Prevention and Rehabilitation” Oncology Grand Rounds. Southwest Cancer Center at University Medical Center, Lubbock, Texas, March 2001
18. “Body mass, physical activity, and sex hormones in postmenopausal breast cancer patients”. American Cancer Society Science Writers Conference, April 2001

19. "Obesity and Women's Cancer" Keynote Lecture, North American Association for the Study of Obesity, October 2001.
20. "Physical Activity and Breast Cancer ", Women's Sports International, St. Louis, June 2002.
21. "Exercise and Breast Cancer", FHCRC Oncology Grand Rounds, October 2002.
22. "Physical Activity after Cancer: Physiologic Outcomes" in Exercise and the Cancer Survivor: What Should we Recommend?, American Dietetic Association Food and Nutrition Conference and Exhibition, Philadephia, October 2002.
23. ** "Exercise and the Prevention of Colorectal Cancer" European School of Oncology Second Colorectal Cancer Conference, Rome, Italy, October 2002.
24. "Energy Balance – an Etiologic Factor in Human Cancer: Randomized Trial of Exercise Effect on Breast Cancer Biomarkers." Oslo Norway, July 2002.
25. "Exercise and Breast Cancer: Impact on Prevention and Recurrence" The Gibson Lecture in Cancer Prevention Endowed Lectureship, University of Virginia School of Medicine, February 26, 2003
26. "Exercise, Body Fat, and Breast Cancer" Florence Ettelson Memorial Lectureship Medicine Grand Rounds, Providence St. Vincent Medical Center, Portland, OR October 2003
27. "Exercise and Breast Cancer" U. Washington Geriatrics Grand Rounds October 2003
28. "Body Mass Index & Breast Cancer Risk" Challenges & Controversies in Breast Cancer, U Washington School of Medicine CME, October 2003
29. "Diet and Physical Activity" 2nd Emerging Trends in Adjuvant Therapy of Breast Cancer Conference, New York City, October 2003.
30. "Exercise in the Prevention of Breast and Colon Cancer" New England American College of Sports Medicine, November, 2003.
31. "Managing Toxicities of Therapy: Weight Loss and Exercise" School of Breast Oncology, November 2003
32. "Exercise and Breast Cancer Prevention" U. Hawaii, January 2004
33. ** "Obesity and Cancer" 2nd International Conference on the Future of Supportive Therapy in Oncology, St. Kitts, Carribean, February 2004
34. "Exercise and Breast Cancer" University of Alabama at Birmingham, CNRC/Nutrition Sciences Seminar Series, March 2004
35. "WHI Estrogen plus Progestin and Breast Cancer Results" FHCRC Gynecologic Cancer Research Program, March 2004
36. ** "Exercise Effects on Total Body Fat, Intra-Abdominal Fat, Insulin, Leptin, and the Metabolic Syndrome in Menopause" Plenary Session, 5th International Symposium on Women's Health and Menopause, Florence, Italy, April 2005
37. "Exercise and Women's Health" University of Virginia, May 2004
38. "Colon ca, biomarkers, and exercise" American College of Sports Medicine, 2004
39. "Obesity Management in Cancer Patients" ASCO, June 2004
40. ** "Effect of Physical Activity on Breast and Colon Cancer Biomarkers" Ireland/Northern Ireland/NCI Cancer Consortium Seminar on Obesity and Cancer, Dublin, Ireland, September 2004
41. "Exercise Trials in Cancer Prevention" AACR Frontiers in Cancer Prevention, Seattle, WA October 2004
42. "Physical Activity, Endogenous Hormones, and Cancer Etiology" Plenary Session AACR Frontiers in Cancer Prevention, Seattle, WA October 2004
43. "Obesity in Breast Cancer Patients" School of Breast Oncology, Atlanta, Georgia, November 2004
44. "Nutrition, Physical Fitness, and Cancer " Aultman Cancer Center, Canton, Ohio, November 2004
45. "Effects of Menopausal Hormone Therapy and Tamoxifen on Mammographic Density" University of Virginia, Department of Radiology, Februrary 2005.
46. "Optimizing Health Outcomes" in Oncology Care in the 21st Century: Integrating Care along the Health Care Continuum, Arthur G. James Cancer Hospital Ohio State University, February 2005
47. "Obesity, Exercise, and Breast Cancer", Tyler, Texas Breast Cancer Conference (talks to oncologists and lay audiences) March 2005
48. "Breast Fitness" talk to women's health providers, Anchorage, Alaska, May 2005
49. "Low Carb Diets: Will They Be Effective in Reducing Breast Cancer Risk?" ASCO, Orlando 2005.
50. ** "Biologic mechanisms involved in the association between physical activity and cancer: results from recent

randomized controlled intervention trials" Eurocancer, Paris, June 2005.
51. ** "Exploring Mechanisms Relating Energy Balance and Cancer" IARC, Lyon, France, June 2005.
52. "Prevention of New and Recurrent Cancers: Lifestyle and Chemoprevention" and "Cancer Screening and Management: The PCP's Role" Issues in Aging Conference, New Orleans, July 2005
53. "Exercise and Cancer Prevention" Rockefeller, NYC, September 2005
54. ** "Open Forum of Breast Health", Mexico City, Mexico, October 2005
55. "Breast Fitness: Exercise for Breast Cancer Patients and Survivors", Cancer Wellness Center Northbrook,IL, November 2005
56. "Obesity in Breast Cancer Patients", School of Breast Oncology, Atlanta GA, November 2005
57. "Insulin Resistance Syndrome and Cancer Risk", International Conference on Metabolic Syndrome, San Francisco, November 2005
58. "Selected Major Findings from the OS Results: Breast Cancer", WHI Conference, Bethesda, February 2006.
59. "Intermediate Endpoints in Energy Balance and Physical Activity Trials" NCI Workshop on State of the Evidence for a Weight Control Trial to Prevent Breast Cancer, Bethesda, March 2006.
60. "Physical Activity and Cancer Recurrence and Survival", Symposium: "Physical Activity across the Cancer Continuum" for the CDC International Congress on Physical Activity and Public Health, Atlanta, April 2006
61. "Exercise, Estrogens, and Breast Cancer: Physical Activity Trials" American College of Sports Medicine, May 2006.
62. "Exercise and Nutrition in Chemoprevention" WCRF/AICR International Research Conference, Washington DC, July 2006.
63. ** "Exercise and Cancer Prevention". National University of Singapore, Singapore, July 2006.
64. ** "Breast Cancer Prevention", "Lifestyle, Diet, and Breast Cancer ", "Lifestyle changes may reduce the risk of recurrence" Mexican Association of Breast Diseases 5th Annual Meeting, Leon, Mexico, August 2006.
65. "WHI and Breast Cancer" Seattle Gynecological Society, Seattle, September, 2006
66. "Physical Activity, Weight Control, and Cancer Prevention" Dana Farber Cancer Center Channing Laboratory and Harvard School of Public Health Seminar Series Speaker, October 2006.
67. "Obesity in Breast Cancer Patients", School of Breast Oncology, Atlanta GA, November 2006
68. "Energy Balance and Cancer: Human Intervention Studies" NCI Energy Balance Working Group, Bethesda, MD, January 2007
69. "Overweight, Obesity, and Sedentary Lifestyle in Breast Cancer Prognosis". Interdisciplinary Science, Health Promotion, and Disease Prevention. Pasadena, CA. May 2, 2007.
70. "Transdisciplinary Research to Elucidate the Pathways Linking Components of Energy Balance to the Cancer Process" Transatlantic Research and Innovation Symposium. Research Triangle Park, North Carolina, May 3, 2007.
71. "Obesity, Physical Activity, & Breast Cancer" University of Washington CNRU May 11, 2007
72. "Women's Health Initiative Clinical Trials" Northwestern University Clinical Research Educational Conference, Chicago, May 18, 2007.
73. "Exercise and Weight Loss in Women and Men" Northwestern University Dept of Preventive Medicine, May 18, 2007.
74. FASEB Energy Balance, Body Fat & Disease, "Exercise and Cancer Prevention", and chair of session "Exercise and Cancer Prevention & Prognosis" Indian Wells, CA, August 2007
75. MD Anderson Cancer Prevention Grand Rounds, "Overweight, Obesity, Physical Activity, and Breast Cancer Prevention" Houston, Sept 2007
76. MD Anderson Integrative Medicine Program Lecture Series talk "Obesity, Weight Loss, and Physical Activity for Cancer Patients and Survivors" Houston, Sept 2007
77. **Breast Health Global Initiative "Primary prevention of breast cancer: lifestyle changes, diet, western lifestyle", Budapest, Hungary, October 2007
78. "Obesity in Breast Cancer Patients", School of Breast Oncology, Atlanta GA, November 2007
79. "Breast Cancer: Women at Risk and New Strategies for Prevention", Practicing Clinicians Exchange, San Francisco, CA November 2007
80. "Exercise Effect on Inflammation and Other Cancer Biomarkers", Southeast ACSM, Birmingham, AL, February 2008
81. "Professional Development for Women", Southeast ACSM, Birmingham, AL, February 2008
82. "Exercise and Body Composition Change Effects on Sex Hormones in Postmenopausal Women", AACR – TREC

Markers & Mediators, Virginia, February 2008
83. "Obesity in Breast Cancer Risk and Prognosis", Case Western University, Cleveland, OH, March 2008
84. "Exercise Interventions in Breast Cancer Prevention and Outcomes", Cleveland, OH, March 2008
85. "TREC Talk", Cancer Prevention and Research Center Retreat, Coeur d' Alene, ID, March 2008
86. ** "Fitness vs. Fatness: Evidence from Epidemiologic and Intervention Studies on the Separate and Combined Effects of Physical Activity and Obesity on Cancer Risk", International Physical Activity Meeting, Amsterdam, April 2008
87. "Influence of Exercise on Immune Function: Possible Link to Breast Cancer", ACSM, Indianapolis, May 2008
88. "Breast Cancer Prevention and Survivorship through Lifestyle and Chemoprevention", Memorial Sloan Kettering Cancer Center, New York City, NY, September 2008
89. ** "Early Detection, Diet, Physical Activity, and Cancer", Women in High Places meeting, Riyadh, Saudia Arabia, October 2008
90. **"Diet and Breast Cancer", Saudi Arabian Cancer Conference, Riyadh, Saudia Arabia, October 2008
91. "Physical Activity & Weight Control in Breast Cancer Prevention & Prognosis", Alaska Conference: "Reducing the Risk, Advancing the Cure: New Recommendations, New Options for Primary Care Providers and Survivors." Televised from Seattle, October 2008
92. "Lessons Learned from Real-Life Lifestyle Interventions", The Obesity Society, Phoenix, AZ, October 2008
93. "Breast Cancer: Weight Loss and Exercise", School of Breast Oncology, Atlanta, GA, November 2008
94. "Fitness vs. Fatness in Breast Cancer Risk and Prognosis", Frontiers of Cancer Prevention, Washington, DC, November 2008
95. "Effects of Exercise and Obesity on Inflammation and Cancer Risk", University of Washington, DERC Seminar Series, February 2009
96. "Does Weight Loss Reduce Cancer Risk?" The Obesity Society, October 2009.
97. Roger E. Moe Award for Translational Research Lecture "Effects of Weight and Physical Activity on Breast Cancer Prognosis" University of Washington *Current Concepts and Challenges in Breast Cancer* October 2009
98. "Lessons learned from physical activity (exercise) interventions" AICR Annual Research Conference on Food, Nutrition, Physical Activity and Cancer, Washington, DC, November 2010
99. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2010
100. "Transdisciplinary studies of weight loss and exercise interventions in women at increased risk for breast cancer", AACR, Washington, DC, April 2010
101. "Exercise Effects on Breast Cancer Biomarkers", International Society for Behavioral Nutrition & Physical Activity, Minneapolis, MN, June 2010
102. **"Physical Activity & Cancer" Lecture, Helsedirektoratet (Directory of Health), Oslo, Norway, December 2010
103. "Physical Activity, Weight Control and Cancer Prevention" Physical Activity and Nutrition seminar series University of Michigan. The School of Kinesiology, February 2011.
104. "Physical Activity in Cancer Prevention" American College of Sports Medicine President's Talk, Denver, CO, June 2011
105. "Breast Cancer Prevention" Foundation for Care Management, Lakewood, WA, January 2011
106. "Breast Cancer Prevention" Foundation for Care Management, Coupeville, WA, February 2011
107. "Inflammation, Insulin, & Obesity in Breast Cancer Survival", University of Texas Southwestern Medical Center, Dallas, Texas, September 2011
108. "Interventions in cancer survivors; issues and challenges in this population", Institute of Medicine Workshop "The Role of Obesity in Cancer Survival and Recurrence", Washington, DC, October 31-November 1, 2011
109. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2011
110. **"Obesity, Physical Activity, & Related Mechanisms in Breast Cancer Survival", Norwegian Congress in Oncology, Oslo, Norway, November 2011
111. "Impact of Obesity on Cancer " Swedish Hospital Medical Center CME, Seattle, WA May 2012
112. "Effects of Weight Loss and Physical Activity on Cancer Risk Factors: Evidence from Randomized Trials", University of Hawaii, July 2012
113. "The Impact of Intentional Weight Loss on Cancer Risk", The Obesity Society, San Antonio, Texas, September 2012
114. "Dietary Weight Loss and Exercise Effects on Metabolic Hormones in Postmenopausal Women", Fred

Hutchinson Cancer Research Center Symposium on Metabolism and Cancer, September 2012
115. **"Lifestyle Modifications to Reduce Cancer Risk and Improve Overall Health", Global Summit on International Breast Health, Vienna, Austria, October 2012
116. **" Medical Perspective on the Influential Role of Obesity in the Risk and Prognosis of Breast Cancer" and "Obesity, chronic diseases and cancer, a common link with lifestyle" Mexican Association of Mastology, Villahermosa, Tabasco, Mexico, October 2012
117. "Effects of Weight Loss and Physical Activity on Cancer Risk Factors: Evidence from Randomized Trials" Oregon Health Sciences University, October 2012
118. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2012
119. "Dietary weight loss and exercise effects on metabolic and sex hormones in postmenopausal women." American Association for Cancer Research, Washington, DC, April 2013
120. "Obesity, Weight Loss, Vitamin D, and Cancer Biomarkers" Fred Hutchinson Cancer Research Center Joint Cancer Prevention/Epidemiology Seminar Series, May 2013
121. **"The WCRF/AICR Continuous Update Project – Systematic Reviews on Nutrition, Physical Activity & Health Outcomes in Cancer Survivors" International Union of Nutrition Scientists (IUNS) 20th International Congress of Nutrition, Granada, Spain, 2013
122. **"Appraisal of Evidence for Obesity Effects on Cancer" IASO/WCRF Obesity, Physical Activity and Cancer, London, 2013
123. "Weight Loss & Exercise Effects on Breast Cancer Biomarkers" University of Illinois Symposium, Chicago, October 2013
124. **"Obesity, Physical Activity and Cancer" State Institute of Diabetes and Endocrinology & Catholic University Post Graduation course on Endocrinology and Metabolism. Rio de Janeiro, Brazil, October 2013
125. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2013
126. "Obesity, Physical Activity and Cancer" Keynote Speaker, The Center for Energy Balance in Cancer Prevention & Survivorship Research Retreat, MD Anderson Cancer Center, February 2014
127. **"Exercise in Cancer Prevention & Survivorship", Athens Institute for Education and Research, 10th Annual International Conference on Kinesiology and Exercise Sciences, Athens, Greece, August 2014
128. **"Weight Loss & Exercise Effects on Cancer Biomarkers," University of Tromso, Norway, September 2014
129. "Breast Cancer Survivors: Findings from the Continuous Update Project," American Institute for Cancer Research Annual Conference, October, 2014.
130. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2014
131. "Obesity, Weight Loss, & Breast Cancer," University of Iowa Diabetes and Obesity Talks Seminar Series, November, 2014
132. "Weight Loss & Exercise Effects on Breast Cancer Biomarkers," Memorial Sloan Kettering Cancer Center, New York, February, 2015.
133. "Physical Activity & Weight Loss Effects on Cancer Biomarkers", NCI Schatzkin Talk, May 2015
134. "Obesity, Weight Loss, Exercise & Breast Cancer" Seattle Cancer Care Alliance, May 2015
135. **"Associations of Weight, Physical Activity, & Diet with Breast Cancer Survival", International Society for Behavioral Nutrition & Physical Activity, Edinburg Scotland, June 2015
136. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2015
137. **"The role of physical activity on cancer risk: epidemiology & molecular mechanisms" WCRF International and World Obesity Federation Joint Conference, September 2016
138. **"Anthropometry: What Can We Measure & What Does It Mean?" WCRF International and World Obesity Federation Joint Conference, September 2016
139. ""Exercise, Weight, and Cancer Risk" University of Alabama Center for Exercise Medicine, Birmingham, September 2016
140. **"Long-term Effects of Exercise & Weight on Breast Cancer Biomarkers" University of Tromso, Norway, October 2016
141. "Exercise, Weight, and Cancer Risk" Roswell Park Prevention Grand Rounds, Buffalo, NY, October 2016
142. "Modifiable Health Behaviors for Cancer Survivors // Health Promotion: Exercise, Physical Rehab" SCCA Cancer Survivorship for Physicians CME, October 2016
143. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2016

144. "Physical Activity & Cancer – What We Know, What We Don't Know" American Institute for Cancer Research AICR's 25th Research Conference, November 2016
145. **"Screening for Breast Cancer: Pro", EuroMedLab, Athens, Greece, June 2017
146. **"Weight Control and Exercise for Breast Cancer Pts & Survivors", Mexican Association of Mastology, 14th National Congress, Guadalajara – México, August, 2017
147. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2017
148. **"Effects of Weight Loss on Cancer Biomarkers, " Canadian Cancer Research Conference, Vancouver, BC, Canada, November 2017
149. "Physical Activity and Diet for Cancer Prevention and Treatment: State of the Evidence," Arizona State University, Tempe, Arizona, February, 2018
150. "Physical Activity for Cancer Prevention and Treatment: State of the Evidence," Wolffe Lecture, American College of Sports Medicine, May 2018
151. ** Diet, Weight & Exercise in Cancer Prevention & Survival: the World Cancer Research Fund Report," Oncology Grand Rounds, BC Cancer, Vancouver, BC, Canada, September 2018
152. **"Physical Activity and Cancer Prevention," National Center for Sport and Exercise Medicine, University of Loughborough, England, July 2018
153. "Weight Control and Exercise for Breast Cancer Prevention," National Cancer Institute, Stars in Nutrition and Cancer lecture, October, 2018

** International Presentations

FUNDED RESEARCH PROJECTS (total dollars unless otherwise noted)

Completed

- A Case-Control Study of Thyroid Cancer in Women, **PI: Anne McTiernan**, American Cancer Society Institutional Grant 1N-26-U, 1979-1982.
- Counseling Strategies for Breast Cancer Risk, PI: Deborah Bowen, PhD, NIH Grant #HG/CA01190-01, 1994-97, $654,409.00.
- Fenfluramine as an Adjunct to Smoking Cessation Therapy, PI: Deborah Bowen, PhD, NIH Grant #R29CA50858, 1990-94.
- Feasibility Study of an Exercise-Diet Program for Breast Cancer Patients, PI: Anne McTiernan, FHCRC Bid and Proposal funds, 1995-1996, $10,000 (direct)
- Echocardiographic Follow-up to a Randomized Trial of Fenfluramine in Women Smokers, PI: Deborah Bowen, PhD, Wyeth Ayerst research contract, 1998, $1,957,627.
- A Randomized Controlled Trial of Fat Reduction and Risk of Proliferative Forms of Benign Breast Disease, WHI Ancillary Study, PI: Tom Rohan, MD; **PI of FHCRC subcontract to U. Toronto: Anne McTiernan,** $13,699.
- Effect of Exercise on Mammogram Densities, **PI: Anne McTiernan,** FHCRC Bid and Proposal funds, 1999-2000.
- SEER Special Studies RFP Interaction of Genetic Susceptibility and Hormonal Exposures in Breast Cancer Prognosis, **PI: Anne McTiernan,** 1999-2001, $137,465.
- SEER Special Studies RFP Mammographic Breast Density and Breast Cancer Prognosis, **PI: Anne McTiernan,** 1999-2001, $123,558.
- Genetic Risk Information for a Defined Populations, PI: Deborah Bowen, PhD, NIH grant #HG/CA1190-01, 1998-2001, $1,143,890.
- Effect of Hormone Replacement Therapy on Mammographic Density, WHI Ancillary Study, PI: Barbara Hulka, MD, MPH; **PI of FHCRC subcontract to UNC Chapel Hill: Anne McTiernan,** 1998-2003, $876,824.
- Effect of Exercise on Sex Hormones in Postmenopausal Women, **PI: Anne McTiernan,** NIH R01CA/AG69334-01A2, 1997-2003, $1,562,811.
- Effect of Exercise on Immune Function in Postmenopausal Women: Supplement to Effect of Exercise on Sex Hormones in Postmenopausal Women, **PI: Anne McTiernan,** NIH R01CA/AG69334-01A2, 1998-2003, $439,112.
- Women's Intervention Nutrition Study (WINS) FHCRC Clinical Center, PI: Alan Kristal; Past-PI, $28,400.
- Exercise Intervention Trial for Colorectal Polyp Patients, **PI: Anne McTiernan,** R01 CA77572-01, 2000-2007, $4,046,212.

- Clinical Coordinating Center, Women's Health Initiative Trial & Observational Study, PI: Ross Prentice; **Role on project: Co-Investigator**, NIH N01-WH-2-2110, 1992-2007+, $112,336,577.
- Randomized, Double-Blind, Placebo Controlled Trial of 4-OH Tamoxifen Gel in Premenopausal Women with 50-80% Density in Breast tissue Based on Digitized Analysis of Screening Mammography, Besins International U.S. Inc. **PI: Anne McTiernan,** 2002-2003, $116,165.
- Seattle Cancer & Aging Program – Pilot: Effect of Exercise on Prostate Cancer Biomarkers: An Ancillary Study to a Randomized Controlled Clinical Trial, PI: Peter Rabinovitch; **PI of Pilot Study: Anne McTiernan**, P20 CA103728, 2004-2006, $39,049.
- Study of Tamoxifen vs. Raloxifene (STAR), PI: R. Clarfeld; **Role on project: Co-Principal Investigator.**
- Exercise and Fitness in Childhood Cancer Survivors, PI: Debra Friedman; **PI of FHCRC Subcontract: Anne McTiernan,** NCI R21, 2004-2006, $23,904 (direct).
- Proteomic Markers of Health Behaviors, PI: Paul Lampe/Yutaka Yasui; **Role on project: Co-Investigator**, NCI-5 R03 CA108339-02, 2004-2006, $173,000.
- Randomized placebo-controlled biomarker modulation trial using Celecoxib in premenopausal women at high risk for breast cancer, SWOG, PI: Powell Brown; **PI of FHCRC subcontract: Anne McTiernan**, NIH/NCI CA37429, 2005-2006, $37,799.
- Effects of Aspirin on Biomarkers of Breast Cancer Risk (Avon Progress for Patients Funds), PI: Nicole Urban**; Role on project: Project Leader, wrote proposal and directed trial**, 2004-2007, $496,238.
- ALPHA Trial: Alberta Physical Activity and Breast Cancer Prevention Trial. Canadian Breast Cancer Research Initiative, PIs: Christine Friedenreich and Kerry Courneya; **Role on project: Co-Investigator**, 2002-2007, $1,104,147.
- Mammographic Density and Invasive Breast Cancer, PI: Etta Pisano, **PI of FHCRC Subcontract: Anne McTiernan**, R01 CA105007-01, 2004-2007, $50,524 (direct).
- Cognitive Effects of Aerobic Exercise for Adults with Impaired Glucose Tolerance: A Controlled Trial (American Diabetes Association), PI: Laura Baker; **Role on project: Co-Investigator**, 2004-2007.
- Cognitive Effects of Aerobic Exercise for Adults with Mild Cognitive Impairment: A Controlled Trial (Alzheimer's Association), PI: Laura Baker; **Role on project: Co-Investigator**, 2004-2007.
- Social and Physical Activity of Childhood Cancer Survivors, PI: Debra Friedman; **Role on project: Co-Investigator**, NIH/NCI CA 104123-01A2, 2005-2007, $107,500.
- UW Multidisciplinary Research Training Grant, PI: R Deyo; Role on project: **Co-Investigator, Mentor**, 1 K12 HD 49100-01, 2004-2009, $1,172,239.
- Epidemiology of Gallbladder Sludge and Stones in Pregnancy, PI: Sum Lee; **Role on project: Co-Investigator**, RO1 DK46890, 2003-2008, $372,840.
- Breast Cancer Prognostic Factors/Pathobiology by Age, PI: Kathi Malone; **Role on project: Co-Investigator**, NCI-1 R01 CA098858-01A2, 2004-2009.
- Seattle TREC Center, **PI: Anne McTiernan,** NIH/NCI U54 CA116847, 09/23/2005 – 08/31/2011, $12,612,045.
- Exercise, Diet, and Postmenopausal Sex Hormones, **PI: Anne McTiernan,** NIH/NCI R01 CA105204**,** 09/01/2004 – 06/30/2011, $3,348,605.
- Reducing Obesity at the Workplace: A Randomized Trial, PI: Shirley Beresford; **Role on project: Co-Investigator**, NIH/NHLBI R01 HL079491, 7/1/2004-6/30/2011.
- Effect of Exercise and Weight Loss on Adipose Tissue Biology, **PI: Anne McTiernan**, NIH/NCI R21 *CA131676*, 05/01/2008 – 04/30/2011, $435,600.
- Effect of Dietary Intervention on Insulin and IGF-1 Receptors in Prostate Cancer (Pacific NW Prostate SPORE pilot project), **PI: Anne McTiernan**, NIH/NCI P50 CA97186, 09/01/2009 – 08/31/2011, $48,836.
- Alberta Physical Activity (ALPHA) and Breast Cancer Prevention Trial: an ancillary study examining androgens, biomarkers of obesity, and inflammation. Alberta Breast Cancer Research Initiative, PI: CM Friedenreich; **Role on project: Co-Investigator**, $170,000.
- Bid & Proposal Funds to Assess Baseline Body Composition, by Dual X-ray Absorptiometry (DXA), in Participants of an Ongoing Clinical Trial (Vitamin D, Diet & Activity Study, ViDA) **PI: Anne McTiernan,** 12/1/2010 – 06/30/2011, $16,000 (direct).
- A Phase III Randomized Controlled Study of Exemestane Versus Placebo in Postmenopausal Women at Increased

Risk of Developing Breast Cancer. **PI of FHCRC Clinic: Anne McTiernan**, National Cancer Institute of Canada**,** 10/2004 – 11/2012, $1,631,150.

- Komen Scientific Advisory Council Award "Vitamin D, Weight Loss, and Breast Cancer Biomarker," **PI: Anne McTiernan,** SAC110024, 07/01/2010 – 06/30/2012, $500,000.
- Weight Loss & Exercise Effects on Telomere Length in Postmenopausal Women, **PI: Anne McTiernan,** NIH/NCI R21 CA155823**,** 12/14/10 – 11/30/12, $428,705.
- Oxidative Stress in Chronic Kidney Disease, University of UW PI: Jonathan Himmelfarb; **Role on project: PI of FHCRC subcontract**, NIH/NHLBI R01 HL070938, 01/01/2011 – 12/31/2012, $197,630 (FHCRC only).
- Komen Scientific Advisory Council Award "Vitamin D, Weight Loss, and Breast Cancer Biomarker," **PI: Anne McTiernan,** SAC110024, 07/01/2012 – 06/30/2013, $225,000.
- NCI: Exercise Effects on Serum Biomarkers of Angiogenesis, PI: Catherine Duggan, PhD; **Role on Project: Co-Investigator & Mentor**, NIH/NCI R03 CA152847, 04/01/2011 – 03/31/2013, $176,000.
- HEAL Follow-up, NIH/NCI Contract. Manuscript Development for the HEAL Study of Breast Cancer Prognosis, **PI: Anne McTiernan,** NCI contract, 10/2012-9/201/3
- Vitamin D Effect on Body Composition During Behavioral Weight Loss in Women, **PI: Anne McTiernan**, NIH 1R03CA162482, 04/01/12 – 03/31/14, $175,000
- Effect of Vitamin D and Weight Loss on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/13-9/30/14, $230,378.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/14-9/30/15, $250,000.
- Weight Loss & Cancer Biomarkers in Women: Oxidative Stress & Inflammation, **PI: Anne McTiernan**, NIH/NCI, 1R01CA161131, 04/15/2012 – 9/30/2015, $863,179.
- Safeway Foundation Assessing Vitamin D, Weight Loss and Breast Cancer Risk Factors, Safeway Foundation, PI: Catherine Duggan, PhD; **Role on Project: Co-Investigator & Mentor**, 7/1/2013 – 6/30/2014, $36,000 (in NCE).
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/15-9/30/16, $250,000.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/16-9/30/17, $250,000.
- Methods for Measurement Error in Physical Activity & Diet, PI: CY Wang; **Role on Project: Co-Investigator,** NIH/NHLBI R21HL121347, 12/1/13-12/31/16, $494,493.

Active

- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/17-9/30/18, $250,000.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/18-9/30/19, $250,000.
- INTense Exercise foR surVivAL among men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL – MCRPC): A Multicenter, Randomized, Controlled, Phase III Study, PI: Jonathan Wright; **Role on Project: Co-Investigator,** Movember, 2016 - .
- Exercise Effects in Men & Women on Colon DNA Methylation, **PI: Anne McTiernan**, NIH/NCI 1R21CA209203-01A1, 3/15/17 – 2/28/19, $421,080.
- Exercise Effects in Men & Women on Colon DNA Methylation, **PI: Anne McTiernan,** NIH/NCI 1R21CA209203-01A1, 3/15/17 – 2/28/19, Administrative supplement, $176,000.
- Impact of an exercise program in cancer patients on chemotherapy treatment, **PI's: Anne McTiernan** & Blair Irwin, Ben Greer SCCA Pilot Study Funds, 9/17-8/18, $50,000 (no cost extension).
- Longitudinal Weight Data from Two Behavioral Weight Loss Randomized Controlled Trial, **PI: Anne McTiernan**, FHCRC Bid & Proposal Funds, 10/17-9/18, $15,000.
- The effects of moderate exercise on distress, quality of life, and biomarkers of angiogenesis and chronic stress in ovarian cancer survivors, NCI R21CA215662-01A1, PI: Kathyrn Pennington; **Role on Project: Co-Investigator**

TEACHING/MENTORING

Junior Faculty

Katy Pennington, MD (School of Medicine, OB/GYN, University of Washington)
Holly Harris, PhD (Epidemiology Program, PHS, FHCRC)
Catherine Duggan, PhD (Epidemiology Program, PHS, FHCRC)
Blair Irwin, MD (Multi-Care, Tacoma, SCCA affiliate)
Jonathan Wright, MD, MPH (School of Medicine, Urology, University of Washington & Epidemiology Program, PHS, FHCRC)

Postdoctoral Fellows

1. Melinda Irwin, PhD (current Full Professor, Yale University)
2. Melanie Palomares, MD, MPH (current faculty City of Hope, Los Angeles)
3. Laura Frank, PhD
4. Page Abramson, PhD
5. Karen Foster-Schubert, MD (current Assistant Professor, U. of Washington)
6. Kristin Campbell, PhD (current Assistant Professor, U. British Columbia)
7. Lisa Cadmus, PhD (current staff scientist U. C. San Diego)
8. Ikuyo Imayama, MD (current medical resident, Seton Hall University, St. Francis Medical Center, Trenton, NJ)
9. Caitlin Mason, PhD (current postdoctoral fellow, FHCRC)

Additional Postdoctoral Fellows Working with My Studies' Data

10. Jean De Dieu Tapsoba, PhD (current postdoctoral fellow, FHCRC; primary mentor is CY Wang, PhD)
11. Aaron Thrift, PhD (current postdoctoral fellow, FHCRC; primary mentor is T. Vaughan, MD)

PhD Committees and Predoctoral Trainee Mentoring

1. Lisa Godefroy Johnson (member of PhD committee)
2. Shelley Slate Tworoger (member of PhD committee)
3. Cara Frankenfeld (member of PhD committee)
4. Victoria M. Chia (member of PhD committee)
5. Lori Williams (member of PhD committee)
6. Angela Kong (co-chair of PhD committee)
7. Babbette Saltzman (member of PhD committee)
8. Anita Iverson (visiting Norwegian predoctoral student 2009-10, advising)
9. Adriana Villasenor (member of PhD committee)
10. Sissi Espetvedt Finstad, MD (Norwegian PhD student, advising)

MS and MPH Committees

1. Margaret Krieg, MD (member of MPH committee)
2. Sylvia Young, MD (chair of MPH committee)
3. Jana Pruski (chair of MPH committee)
4. Melanie Palomares (chair of MPH committee)
5. Susan Stanford (member of MPH committee)
6. Melinda Irwin, PhD (chair of MPH committee)
7. Andrew Shors, MD (member of MPH committee)
8. Libbby Morimoto (member of M.S. committee)
9. Breanna Mitchell (member of M.S. committee)
10. Erin Aiello (chair of MPH committee)
11. Erin Shade (member of M.S. committee)
12. Julie Meyers (member of M.S. committee)
13. Manish Mohanka (chair of MPH committee)
14. Vivian Hawkins (chair of MPH committee)
15. Isaac Rhew (member of MPH committee)
16. Ann Ready (member of MPH committee)

17. Alanna Boynton (member of MS committee)
18. Heather Hildebrant (member of MPH committee)
19. Jo Henderson (chair of MPH committee)
20. Laura Hooper (member of MPH committee)
21. Kristen Sipsma (member of MPH committee)
22. Karen Foster-Schubert (chair of MS committee)

Advising: Medical Students Research (University of Washington ISMS): Jennifer Rupert, Erin Griffith, Kelley D. Pratt, Maegan Ashworth
Post-Graduate Physician Training in Cancer Prevention & Control (FHCRC): Elliott Rosenberg, MD, MPH, Mary Ann Gilligan, MD, MPH, Maureen Brown, MD
Formal Career Development Mentoring: Karen Foster- Schubert, MD, University of Washington NIH K-12 Fellow 2005-2010; Karen Mustian, PhD University of Rochester NCI Cancer Control Clinical Research Training Program 2004-
FHCRC scientists mentoring: Neli Ulrich, PhD, Rebecca Rudolph, MD, MPH, AnneClaire DeRoos, PhD, Alyson Littman, PhD, Jonathan Wright, MD, MPH, Catherine Duggan, PhD, Larissa Korde, MD
Individual Study Credits

Course	Title	Credits	Years
Epi 499	Undergraduate Research	Var	1997-2005
Epi 600	Graduate Study/Research	Var	1997-2005
Epi 700	Masters Research	Var	1998-2005
Cancer Epi	guest lecture	1999, 2002-2005	

Continuing Medical Education Teaching

- Breast Cancer in Young Women, University of Washington Continuing Education Conference, August 6, 1994, Depts. of Surgery and Medicine.
- Current Concepts in the Early Detection of Breast Cancer, Multicare, Madigan Army Medical Center, and American Cancer Society 3rd Annual Oncology Conference, April 11, 1995.
- Current Concepts in Breast Cancer – 1997, University of Washington Continuing Medical Education, October, 1997, 1999, 2000 (session moderator), 2001, 2003, 2009, 2010
- “Update to the Women’s Health Initiative” March 18, 2001, University of Washington talk to IM, GYN, FM residents.

Clinical Teaching (U. of Washington School of Medicine)

- Attending Physician, Adult Medical Center, Harborview Medical Center, 1992-95 – supervised internal medicine residents in primary care setting.
- Mentoring and training geriatric fellow, Dr. Michi Yukawa, in exercise tolerance testing and testing VO2 max (1999)

Other Academic
Primary Opponent, PhD Thesis Defense, Aina Emaus, University of Oslo, Norway (thesis chair, Inger Thune) 2009

FHCRC SERVICE

- Director, Prevention Center Shared Resource, 2001-2012
- Chair or Member of several faculty promotion committees and 5-year review committees
- Reviewer for CCSG renewal: 2013, 2018
- Member, Scientific Advisory Committee for the Seattle Cancer Care Alliance Prevention Clinic
- Member, Research Trials Office Oversight Committee, 2003 – 2005
- Member, Fred Hutchinson Cancer Research Center Institutional Review Board, 1984-5; 2002 - 2003
- Member, FHCRC Health Care Task Force, 1996
- Member, Clinical Protocol Scientific Review and Monitoring Committee, 1996- 1997
- Organizer, FHCRC Public Health Sciences Hormone Special Interest Group 1995-96
- Member, Seattle Breast Cancer Program Executive Committee, 1998 - 2000
- Member, Ad-Hoc Committee on Improvements in Public Health Sciences Procedures, 1998
- Member, CSS Advisory Committee, 1999 – 2000

- Nutritional/Hormonal Biomarkers group, 2001 – 2002
- Member, CDS Users Group, 2001 – 2002

UNIVERSITY OF WASHINGTON SERVICE

- Reviewer, Royalty Research Fund, Spring, 1997
- U. Washington Breast Cancer Update 2000 Continuing Medical Education – session moderator

PROFESSIONALLY-RELATED COMMUNITY SERVICE

- Medical Advisory Board, Team Survivor Northwest 1997-
- Professional Advisory Committee, Breastcancer.org, 2003-

LAY AUDIENCE PRESENTATIONS

- National Council of Jewish Women, Seattle Section, "Women's Health Initiative", Nov 1992
- Nordstrom's "Face of Breast Cancer" breast cancer awareness seminar, October 1997
- Danskin Women's Triathalon, 8/15/98
- Afternoon of Hope, Horizon of Hope National Charity Campaign, Longaberger Co., FHCRC, 8/29/98
- Media roundtable, Women's Health Initiative, December, 1995
- Breast Cancer Forum: Clinical Implications of Current Research, FHCRC, 10/8/98
- Women's Health Issues Panel, The Healthy Living Expo, Seattle, WA, 2/7/99
- Virginia Mason Hospital Breast Cancer Support Group "Weight Control and Cancer Survival" September 1999.
- FHCRC Volunteer Conference "Breast Cancer Risk Factors" May 2000.
- FHCRC Women's Health Series "Exercise and Breast Cancer" April 2000.
- Bellevue Rotary Club, "Exercise and Breast Cancer" October 2000.
- Cardio Pulmonary Rehabilitation InstituteOncology Rehabilitation, Lubbock Texas, "Exercise for Breast Cancer Prevention and Rehabilitation", March 2001
- Greater Cincinnati Breast Cancer Association, October 2001.
- FHCRC Community Lecture "Exercise for Breast and Colon Cancer Prevention" November 2001
- Providence/St. Vincent Medical Center, Portland, OR October 2003
- Women's Health Day, Anchorage, Alaska 2005
- Cancer Wellness Center, Northbrook, IL 2005

MEDIA

- Media (TV) interviews on physical activity, obesity, vitamin D, sleep, cancer: Today Show (NBC); MSNBC News Show; ABC News w/Peter Jennings; ABC World News Tonight; CBS Evening News; CBS News; Seattle KOMO, KIRO, KING, FOX13; WZTV-FOX, KOCO-ABC, WFLA-NBC, WBTV-CBS, WLUK-FOX
- Media (radio): KJZZ, Canadian health radio talk show; numerous Seattle-area radio interviews
- Media (print) –Prevention Magazine, American Health Magazine, Time Magazine, Parents' Magazine, Family Circle, Associated Press, Time, Women's World, Cosmopolitan, Glamour, Self, Reader's Digest, New York Times, Wall Street Journal, LA Times, Parade Magazine, Seattle Times Pacific Magazine, USA Today, U.S. News and World Report, Health Magazine, Seattle Magazine, Self, More and others
- Several on-line news media each year
- "Preventing Breast Cancer" written commentary for ABC.com, April 2002.
- Ivanhoe National TV Productions specials on Breastfeeding, Breast Cancer, and Breast Gel Study September 2002

Exhibit 23

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

RULE 26 EXPERT REPORT OF
SONAL SINGH, MD, MPH

Sonal Singh

Date: November 16, 2018

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Sonal Singh, MD, MPH

TALCUM POWDER PRODUCTS AND RISK OF OVARIAN CANCER

EXPERT REPORT

Prepared by

Sonal Singh, MD, MPH

University of Massachusetts School of Medicine

Nov 16, 2018

Table of Contents

I. INTRODUCTION AND SUMMARY.

I have been retained to review scientific evidence and analyze the epidemiological data and, based on these data and other relevant evidence, to provide my professional opinion about whether talcum powder products are causally related to ovarian cancer. I have used a weight of evidence approach in examining the causal relationship between talcum powder products and ovarian cancer. I have relied upon my own systematic review of the literature and the cumulative body of evidence as the basis upon which I provide my opinions. This included gathering all relevant data based on *in vitro*, animal, and human epidemiologic studies on this topic. Although the weight of my opinions is derived from findings published in the peer-reviewed literature, relevant unpublished documents are also noted when applicable. The individual studies were examined for both reliability and validity noting their strengths and limitations. The cumulative body of evidence was then synthesized and examined and weighed using a widely accepted organizing framework- the Bradford Hill approach. (1). Using these materials, my education, and my prior clinical and research experiences, I have employed the methods generally accepted by the scientific community that would be used to develop a peer-reviewed manuscript.

In summary, it is my opinion, to a reasonable degree of scientific and medical certainty, that talcum powder products, specifically here Johnson's Baby Powder and Shower to Shower, can cause ovarian cancer. This finding is based on the totality of the medical and scientific evidence from meta-analysis, and consistent findings of a statistically significantly increased risk in observational studies, evidence of retrograde migration and inhalation of talc, presence of known or suspected carcinogens in Talcum Powder Products, and inflammatory tissue response that initiates multiple pathways and biological mechanisms by which talcum powder products can cause ovarian cancer While these factors carry the most weight in my assessment, available data on the biological gradient of Talc exposure and ovarian cancer (dose response) also support my opinion.

II. BACKGROUND AND QUALIFICATIONS.

I am an Associate Professor in the Department of Family Medicine and Community Health and the Meyers Primary Care Institute, with a joint appointment in the Department of Quantitative Health Sciences at the University of Massachusetts Medical School, Massachusetts. I received

my M.B.B.S. (equivalent to M.D.) in 1998 from Patna Medical College, India. I then completed my internal medicine internship and residency in the Department of Medicine at the Unity Health Center, affiliated with the University of Rochester School of Medicine in 2005. Subsequently, I served on the Faculty as an Instructor of Medicine at Wake Forest University until 2007, and then as an Assistant Professor of Medicine in 2007. I received a joint appointment as an Assistant Professor of Epidemiology at Wake Forest University in 2008. While on the faculty at Wake Forest University, I obtained my master's in public health at Johns Hopkins University in 2008. I was an Assistant Professor in the School of Medicine at Johns Hopkins University as a recipient of the NIH Johns Hopkins Clinical Research Scholars Award in 2009. I held joint appointments in the Department of International Health and Health Policy and Managements and served as the Associate Director at the Center for Drug Safety and Effectiveness at Johns Hopkins University until 2016.

In my current position, I devote most of my professional time to epidemiologic research. I conduct clinical research with a focus on drug safety, evidence synthesis, and shared decision making. The major focus of my research is understanding the adverse effects of pharmacologic therapies. The remainder of my professional effort is dedicated to practicing general medicine and teaching activities. I have taught courses in systematic reviews, clinical epidemiology, pharmacoepidemiology, and the practice of internal medicine to medical students, interns, residents, and public health students at Johns Hopkins University and Wake Forest University. I have taught courses in clinical epidemiology and pharmacoepidemiology to researchers in the Bloomberg School of Public Health at Johns Hopkins University

I have served as an advisor to the World Bank, WHO International Agency for Research on Cancer and various pharmaceutical firms. I was part of World Health Organization International Agency for Research (WHO-IARC) panel which evaluated the carcinogenicity of various drugs and herbal products. (2). I currently serve as a member of the American College of Chest Physicians Guideline Panel. I have also been part of a panel that developed the PRISMA-HARMS (Preferred Item for Reporting Harm in Systematic Reviews and Meta-Analyses) checklist with an aim to improve the reporting of systematic reviews and meta-analysis of adverse effects. (3). My research has been funded by the Food and Drug Administration, the Agency for Health Care Research and Quality, the National Institute of Health and the Patient Centered Outcomes Research Institute. I am a recipient of numerous awards including the prestigious Johns Hopkins Clinical Research Scholars Award from the

National Institute of Health and the Tinsley R. Harrison Master Teachers Award at Wake Forest University School of Medicine. My systematic review on varenicline and the risk of cardiovascular events published in the prestigious Canadian Medical Association Journal was awarded the Best Research Paper of the year among hundreds of articles submitted to the Journal. I also serve as a peer reviewer for more than 50 journals and serve on the editorial board of prominent journals such as *BMJ Evidence Based Medicine*. I have reviewed grants for numerous federal and international organizations. I have conducted several epidemiological studies and systematic reviews and meta-analysis featured in prominent medical journals such as the *Journal of the American Medical Association* and the *British Medical Journal*. I have authored or co-authored more than 100 original peer-reviewed scientific articles and my work has been cited more than 13,000 times and my h-index is 48 [h number of papers which has been cited by others at least h times]. My work has been featured in *Science, Journal of the American Medical Association, British Medical Journal, and the Lancet*, as well as media outlets such as the NYTIMES, *Wall Street Journal* and *Washington Post*.

This background provides experise in the use of epidemiological research methods in diverse settings, and in the clinical practice of medicine, both relevant to the present scenario. I have charged a rate of $600.00 per hour in the preparation of this report. Attached as Exhibit A is a copy of my curriculum vitae.

III. PUBLICATIONS.

Below is a representative sampling of those articles published in leading medical journals such as *Journal of American Medical Association, Journal of American Medical Association-Internal Medicine,* and *British Medical Journal*. Please refer to my attached curriculum vitae for a complete listing of all publications.

- Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone- A systematic review and meta-analysis. *Journal of the American Medical Association* 2007; 298: 1189-1195.
- Singh S, Loke YK. Furberg CD. Inhaled anticholinergics and the risk of major adverse cardiovascular events in Patients with Chronic Obstructive Pulmonary Disease: A systematic Review and Meta-analysis. *Journal of the American Medical Association* 2008; 300: 1439-1450. (CME Article in JAMA).

- Mills EJ, Wu P, Chong G, Ghement I, Singh S, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170 255 patients from 76 randomized trials. Q J Med 2011; 104: 109-24.
- Singh S, Loke YK, Enright P, Furberg CD. Mortality Associated with Tiotropium Respimat® in Patients with Chronic Obstructive Pulmonary Disease- A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *British Medical Journal* 2011; 342: d3215.
- Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events with Varenicline: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Canadian Medical Association Journal* 2011; 1831359-66. (with an editorial by JT Hays. Varenicline for smoking cessation. Is it a heart breaker?)- Best Research paper of the year award.
- Singh S, Loke YK. Drug Safety Assessment in Clinical Trials: Methodologic Challenges and Opportunities. Trials 2012, 13: 138.
- Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike Peptide 1-Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Ovarian cancer Mellitus: A Population-Based Matched Case-Control Study. *Journal of the American Medical Association Intern Med*. 2013 25:1-6.
- Grosse Y, Loomis D, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K; International Agency for Research on Cancer Monograph Working Group. Collaborators: Stewart BW, Biggar RJ, Lachenmeier DW, Singh S, Tsuda H, Baguley B, Marques MM, Tseng CH, Knight TL, Beland FA, Betz JM, Carcache de Blanco EJ, Cunningham ML, Dunnick JK, Guo L, Jameson CW, Karagas M, Lunn RM, McCormick DL, Witt KL, Zhou S. Carcinogenicity of some drugs and herbal products. *Lancet Oncol*. 2013; 14(9):807-8.
- Zorzela, L., Loke, Y.K., Ioannidis, J.P., Golder, S., Santaguida, P., Altman, D.G., Moher, D., Vohra, S., Boon, H., Clark, J., Derry, S., Gallivan, J., Gardiner, P., Gøtzsche, P., Loder, E., Napoli, M., Pilkington, K., Shekelle, P., Singh S, Witt, C., Lasserson, T., Wu, T., Shamseer, L., Mulrow, C. PRISMA harms checklist: improving harms reporting in systematic reviews. *British Medical Journal* 2016;352: i157.
- Onasanya O, Iyer G, Lucas E, Lin D, Singh S, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. *Lancet Diabetes Endocrinol*. 2016 Nov;4(11):943-956.
- Alexander GC, Iyer G, Lucas E, Lin D, Singh S. Cardiovascular risks of exogenous testosterone among men. *Am J Med*. 2017 Dec;130(12):1449-1457.

IV. STUDY DESIGN CONSIDERATIONS.

I will examine the strengths and weaknesses of the study designs that are relevant to the present scenario. Each of the study-types discussed below has its advantages and disadvantages. Every study is subject to biases and error; none is appropriate and feasible for every situation. Instead, the evidentiary value of each study must be assessed and weighed on an individual basis, and in the context of the totality of the body of literature or scientific studies.

IV.I Randomized controlled trials. In double blind randomized controlled trials (RCTs) both the investigator and the participant are blinded to treatment assignment. All characteristics whether known or unknown, are evenly distributed at random between the intervention and placebo arm. Thus, if there are differences in incidence of outcome, it can be inferred to be a consequence of the exposure itself (i.e. causative).

However, the prospective nature of RCTs also results in several significant drawbacks for effects that are rare and/or slow to develop, like ovarian cancer. In addition to the ethical difficulties of administering a substance that may be harmful, such as talcum powder products, it is difficult prospectively to ensure study-subject compliance over the decade-plus timeframes required to assess ovarian cancer risk, and obviously impractical to have researchers administer a daily perineal talc application to study subjects. Similarly, there is no mechanism by which to randomly assign participants for non-modifiable exposures or the event may be sufficiently rare, such as in the present case of ovarian cancer to be evaluated in a randomized trial. The definitive randomized controlled trial in which patients would be randomized to talcum powder products and/or placebo and measure the outcome of ovarian cancer would be ideal. However, such a randomized trial does not exist, and such a randomized trial would be unethical.[1] Then again, randomized clinical trials are not necessary to establish causal evidence of harm. For instance, there is no randomized trial which supports the causal role of smoking in lung cancer. As a result, to address this question, we must rely on other study designs including observational studies and their meta-analysis to draw inferences on causation. The preponderance of evidence we have on harms of products are derived from such epidemiological studies.

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[1] Defendants here have admitted this fact. Deposition of Linda Loretz 562:14-563:6 (October 1, 2018) (4); Deposition of Joshua Muscat 408:21-410:20 (September 25, 2018) (5).

IV.II Systematic reviews and Meta-analysis. A systematic review and meta-analysis is a study design wherein systematic searches are carried out to identify studies reporting on a question of interest. Systematic reviews provide a high level of evidence when evaluating the effect of interventions. (6).

The meta-analytic point estimate represents the sum of evidence from all the included studies. When individual studies may be underpowered to detect an effect, meta-analysis of cumulative studies may allow one to distinguish whether the entire body of evidence supports the presence or argues against evidence of a causal association. Apart from the P-value as a measure of statistical significance, the confidence intervals are used to assess the statistical variability around the estimate. In a meta-analysis the studies are weighted by the sample size of included studies with larger studies contributing more weight to the final estimate. Studies are examined to determine whether the findings are clinically and statistically homogenous or heterogenous. Clinical heterogeneity includes any differences in populations and interventions. It is also important to evaluate statistical heterogeneity among studies included in the meta-analysis. (7). Although some amount of variation in individual estimates of treatment effect is expected by chance, the excess of variation which cannot be explained by chance alone is referred to as statistical heterogeneity. I^2 is used as a measure of *statistical heterogeneity*—a percent of variation due to heterogeneity compared to chance, the higher the value the more the proportion of statistical heterogeneity.

The different approaches to modelling data across studies may yield slightly different results. Fixed effects meta-analysis which assumes that all the studies are measuring the same effect yield tighter confidence intervals, whereas random effects meta-analysis which assume that studies are measuring different effects in the population yield more conservative effects. Random-effects models may be more appropriate when the amount of statistical heterogeneity is high. Some amount of heterogeneity is expected when the database includes observational studies.

However, it must be noted that while meta-analysis can overcome issues of limited statistical power and provide information on consistency or inconsistency of effects, one needs to carefully examine the individual studies for their limitations and susceptibility to bias and confounding.

Thus, for example, if a study is too short to detect the effect in question, then even a patient-level pooled analysis of several such studies will very likely fail to detect a true causal relationship, even when one exists. This is an illustration of why it is important to consider study design, bias, and confounding in weighing the results from both individual studies and their meta-analysis. Systematic reviews are also susceptible to various publication and funding biases which need to be considered in interpreting results.

Meta-regression in using summary or group level published data may be susceptible to ecological or group level biases and result in spurious conclusions. (8). As a result, it is not recommended to evaluate the association between treatment effect, such as the difference in the risk of ovarian cancer, and participant characteristics at the study level (e.g., mean age of all participants) using aggregate level data, (9) as these may be susceptible to group level or ecological biases. An individual participant pooled analysis in which investigators have access to the patient-level data, such as that by Terry et al. discussed below, (10) is considered of higher quality than meta-analysis of summary data and provides the ability to reliably assess the effect of other patient and outcome related variables.

Umbrella reviews and overviews of systematic reviews. An umbrella review systematically collects and reviews evidence from multiple systematic reviews and meta-analysis and allows integration of evidence from multiple systematic reviews and meta-analysis, (11) to offer a much broader view of the evidence landscape. Individual systematic reviews and/or meta-analysis included in an umbrella review or overview should be critically appraised for quality. The 11-item critical appraisal tool AMSTAR (Assessing the Methodological Quality of Systematic Reviews) is a reliable and valid tool which provides an assessment of the quality of included systematic reviews and meta-analysis in an overview. (12).

What is the precise causal question or the hypothesis being tested? One cannot interpret the scientific evidence without being precise about the causal question that is being addressed when evaluating the association between any exposure and an outcome in any epidemiologic study. An exclusively narrowly framed hypothesis (e.g., evaluating only one route of exposure such as using talcum powder on contraceptive diaphragm), (13) while disregarding other important and relevant routes and mechanisms of exposure, is <u>inherently limited by design.</u> Since we may not have a complete picture of the underlying mechanisms or the timings of risk of products at the

time of study design, it is even more critical that studies on safety evaluate all potential routes of exposure.

IV.III. Cohort and Case-Control Studies. There are several considerations in interpreting data from prospective or retrospective observational studies or case-control studies. However, it is important to consider issues of study design, random error, systematic error, bias, and confounding in the interpretation of data. Random errors are statistical fluctuations in the measured data due to the limitations of the measurement instrument. They may occur in both direction because of the inability to measure exposure and outcomes in precisely the same manner. There is also the possibility of measurement error in the measurement of outcome and exposure in both study designs. If the measurement error is non-differential, such misclassification of exposure or outcomes usually biases findings towards the null. Systematic errors, by contrast, are reproducible inaccuracies that are consistently in the same direction, often due to a problem which persists throughout the entire study and are difficult to correct.

Case-control studies involve subjects diagnosed with the disease at issue, such as ovarian cancer (the “cases”), and a suitable number of subjects without the disease (the “controls”). Exposure is ascertained retrospectively among both cases and controls. The results are then analyzed to see if there is an association between the exposure and the disease. In contrast, prospective cohort studies are study designs in which subjects with and without the exposure of interest are recruited and followed up in time for the development of outcomes. This study design establishes temporality wherein the exposure precedes the outcome. It is important to determine the latency and induction between the exposure and the disease to assess the duration of follow-up. As an example, a 12-month follow-up study to evaluate the association between exposure to smoking and lung cancer would be unlikely to demonstrate an increase in the risk of lung cancer.

There are several strengths to the case-control design including the ability to ascertain long-term exposure-outcome relationships, particularly important to the present scenario because ovarian cancer develops over many years. Once cases and controls have been established, one can evaluate the association between multiple exposures and outcomes. In contrast, prospective cohort studies may be limited by the short-duration of follow-up which may be insufficient to ascertain the effect of exposure on long-term outcomes and bias their findings towards the null. Secondly, for relatively rare diseases, such as ovarian cancer, case-control studies are more

efficient. Because we are looking at the incidence of disease between the two arms of a study, a cohort study may have limited statistical power regardless of the actual number of subjects enrolled if the number of cases is small. For example, the Nurses' Health Study recruited almost 80,000 participants for only 307 cases of ovarian cancer. (14).

Both study designs are susceptible to selection bias when the selection of the participants into the study (or their likelihood of being retained in a cohort study) leads to a result that is different from the result had we enrolled the entire target population. In other words, the exposure-outcome relationship in controls or cases may be different from the target population. This can arise due to selection of controls not representative of the target population, non-response that is related to exposure and outcome, or differential loss to follow-up in a cohort study related to exposure and outcome status. Selection bias can bias findings either away from the null or towards the null.

Case-control studies, by their design, are generally not blinded and are also susceptible to bias as a result. They are also susceptible to recall bias, i.e. the concern that subjects with the disease may be more diligent in recollecting past uses. However, the degree of recall bias will depend on the type of exposure with chronic daily long-term exposures, such as talcum powder product use, being less likely to be subject to recall bias than intermittent short-term exposures. In contrast, prospective cohort studies in which subjects are recruited and then followed up for the development of outcomes are less susceptible to recall bias.

In addition, there is the issue of what may be called "behavior change" bias in cohort studies which may also bias their findings towards the null if exposure is only ascertained at baseline and not updated during follow up. This bias towards the null reduces the apparent effect of the exposure on the outcome. For example, if the subjects accurately report their talcum powder product use (or lack there-of) at baseline, but there is no follow-up, then the "ever" users' status will still be correct at the end of the study, because once having used talc, their "ever" status cannot change. This will not be true, however, of the "never" users; if they subsequently use talc, then without follow-up, their status will still be incorrectly recorded as "never." If there is a true causal connection, some ovarian cancers caused in the "never" category will, in fact, belong in the "ever" category, potentially biasing the study towards the null. Cohort studies are also susceptible to attrition bias and efforts should be used to minimize loss to follow-up. The main strengths of cohort studies are that if an effect (after adjusting for other confounding

factors) is found despite these biases towards the null, then it is more likely to be a causal relationship; the limitations being that they are less sensitive to determining a causal relationship. Case-control studies are based on past behavior and are not affected by this bias. Cohort studies are also susceptible to several prevalent user biases including potential bias due depletion of susceptibles. (15). A cohort study evaluating the association between talc use and ovarian cancer which limits the analysis to prevalent users (rather than new users), may largely be composed of survivors of the early effect of talc exposure on ovarian cancer, since new users who developed ovarian cancer after talc exposure may be ineligible for inclusion. This will potentially bias the estimates towards the null.

One important distinction to note is between risk factors for the disease and confounders. (16). A risk factor is an exposure which may explain the development or cause of disease in the population. These could be potentially modifiable or non-modifiable risk factors such as genetic risk factors. Confounding represents a special case of bias that results when the relationship between the risk factor -disease relationship is altered. A variable is considered a confounder only when ALL three criteria are present: a) the confounder is associated with the exposure in the population; b) the variable is related to the disease in the population; and c) the variable is not a link in the causal pathway to the disease. Risk factors that do not meet all the above criterion are not considered confounders of the exposure-outcome relationships (and thus may not require adjustment in the analysis).

Observational studies may also be susceptible to unmeasured confounding. Importantly, the potential for confounding does not mean that such a confounding exists. To address bias, confounders of the disease-outcome relationship need to be adjusted for in the analysis of epidemiologic studies. The methods for adjustment for known confounders include regression or propensity score methods. In establishing the effect of any exposure on an outcome it is important to disentangle the direct effect of an exposure of an outcome vs the indirect effect because of some mediators. The strength of association, in and of itself, does not denote whether a risk factor causes the disease. It is reflective of the background rate of the disease in the population and the relative risk of other competing risk factors. When the strength of association is weak, restricting the disease to a low risk population with low background rates of the diseases will magnify the association due to lack of competition among risk factors. (16)

One must be careful in interpreting data from subgroup analysis, such as analysis of various dose categories or age or ethnic groups, such as the case here with pre-menopausal women vs post-menopausal women or subgroup of women stratified by age, sex and ethnicity. The results of tests of interaction are important in interpreting data from such studies. If the test of interaction is not significant, this suggests that there is a lack of significant difference between the two groups. However, such subgroup tests can be underpowered because of reduction in sample size. Additionally, while a study may be internally valid it may not be generalizable to participants in the overall population beyond those included in the study. As an example, the cohort study of post-menopausal women reporting a non-significantly increased risk of ovarian cancer with genital talc use may not be generalizable to premenopausal women. (17). Despite the limitations noted above, most of our knowledge of the adverse effects of therapies has been derived from observational studies, since randomized controlled trials are not practical for several agents and rare outcomes.

It is also important to draw attention to the proper interpretation of P-values, confidence intervals and statistical significance. (18). I have followed the general principles laid out by the American Statistical Association on the interpretation of P-values and statistical significance. P-value can only indicate how incompatible data are with a statistical model. P-values do not indicate the probability that the studied hypothesis is true or the probability that data were produced by random chance alone. A P-value does not measure the size of an effect or the importance of a result and undue reliance should not be placed on whether a P-value passes a specific threshold. Full reporting and transparency are needed for interpretation of results. Confidence intervals (CI) measure statistical significance, (19) and indicate the precision and degree of uncertainty associated with a sample statistic. A 95% CI means that if we used the same sampling method to select different samples and computed an interval estimate for each sample, we would expect the true population parameter to fall within the interval estimates 95% of the time. CIs that remain elevated above 1 for relative risks (RRs) or odds ratios (ORs) are considered statistically significant. A narrow CI indicates a relatively higher level of precision. Non-overlapping CIs across two studies suggest a statistically significant difference between the study findings, whereas overlapping CIs may suggest consistent results. Thus, it is not necessary, and it is highly unlikely to have identical point estimates across studies to establish the presence of a consistent exposure-outcome association.

V. EPIDEMIOLOGY AND PATHOGENESIS OF OVARIAN CANCER.

Ovarian cancer is the most lethal gynecologic cancer in women. It is the leading cause of cancer death among gynecologic cancer in the US and the fifth most common cause of cancer with more than 14,000 deaths per year. The incidence is 11.4 cases per 100,000 women per year, with a mortality rate of 7.4 deaths per 100,000 women. (20). Approximately 1.3 percent of women will be diagnosed with ovarian cancer at some point during their lifetime. Approximately 22,400 new cases of ovarian cancer would be diagnosed in the US in 2017 with 14,080 deaths. (21).

Most women are diagnosed at an advanced stage of the disease and it is usually asymptomatic but may present as abdominal distention, bloating, and in a minority of cases vaginal bleeding. The prognosis is relatively poor when it presents at the advance stage where therapeutic options including chemotherapy offer little benefit. As discussed in more detail in Section X below, inflammation is known to play an important role in the pathogenesis of ovarian epithelial cancer through a mechanism of cell proliferation, oxidative stress DNA damage and gene mutations.

VI. WHAT CONSTITUTES COSMETIC TALCUM POWDER PRODUCTS?

- While I will examine the evidence of talcum powder products and their causal association with ovarian cancer, ascertaining what constitutes "talcum powder" it is important to emphasize that Talcum powder cosmetic products are not "pure talc." The evidence I reviewed demonstrates talcum powder products contain asbestos, fibrous talc, heavy metals such as cobalt, chromium, nickel, and various fragrance chemicals (22)(23). This report evaluates the risk of ovarian cancer associated with talcum powder products and its constituents. When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products and all constituent elements contained within.

- Talc is a naturally occurring mineral and its chemical composition is hydrous magnesium silicate with a chemical formula of Mg3Si4O10(OH)2. In its natural form, talc may contain asbestos, also a naturally occurring silicate mineral, with a different crystal structure. Both talc and asbestos belong to the family of silicates that may occur in fibrous form, which is known to cause cancer. The structure of talc is characterized by a hexagonal sheet arrangement of silicon oxygen tetrahedral groups in a common plane. This results in a double-sheeted structure where the sheets are held together by weak van der Waals bonds. Talc consists mostly of these plate-

like structures ("platy talc") but talc can occur in fibrous form. Talc fibers are like asbestos fibers in size and shape. (22, 24).

- Despite claims that talcum powder products manufactured after the mid-1970s were "asbestos free," published articles, internal company documents, and testing of historical samples I reviewed demonstrate that talcum powder products can contain asbestos and other carcinogenic constituents as discussed below. For example, talc powders from national and international markets were analyzed by Paoletti et al. in a 1983 study to assess fiber content. (25). Samples of talc powders demonstrated fiber contents up to 30% of total particles. About half of the talc powders revealed the presence of asbestos. In some samples, a very high level of asbestos was revealed. (25). Consistently, the 1991 Blount study also found asbestos in cosmetic talcum powder. (26). In a recent deposition, the author of the 1991 study testified she had detected specifically in Johnsons and Johnsons baby powder. (27).

- Although the FDA conducted a survey of talc manufacturers in 2009-2010 and found no asbestos fibers or structures in any of the samples of cosmetic-grade raw material talc or cosmetic products containing talc, (28) the results were limited; only four out of nine talc suppliers submitted samples, and the number of products tested was low. The failure to detect asbestos could either be due to the technique used or the use of a non-representative sample. The FDA itself noted the study could not "prove that most or all talc or talc-containing cosmetic grade products currently marketed in the United States are likely to be free of asbestos contamination." (29).

- I reviewed Longo et al.'s report from August 2017 where he tested 30 bottles of Johnson's Baby Powder. (30). They found 17 samples contained detectable amounts of asbestos. They also found half of the samples contained fibrous talc. I also reviewed two additional reports from Dr. Longo where he found fibrous talc and asbestos in Johnson's Baby Powder. (31, 32). I reviewed the depositions and exhibits of Dr. John Hopkins, corporate representative for Johnson and Johnson, who testified to numerous positive tests for asbestos and fibrous talc. (33).

- In a recent report, Longo et al. (34) estimates that 37 out of 56 random samples (66%) of bottles of talcum powder products tested contain asbestos, which indicates that approximately 2 out of 3 bottles of talcum powder containing products are contaminated with asbestos. Talcum powder products are generally used by women habitually for months or years, rather than a

single application or a single bottle of use. Each successive use of a bottle of talcum powder product_by an individual further accentuates the cumulative probability of their exposure to asbestos, beyond the probability conferred by the use of a single bottle. I reserve the right to supplement my report in order to estimate this probability of exposure to asbestos through habitual use of talcum powder products contaminated with asbestos, once the analysis of additional samples of talc is complete. Longo et al. also estimates that 41 of 42 random samples of bottles of talcum powder products tested contain fibrous talc. I reserve the right to supplement my report in order to estimate this probability of exposure to fibrous talc through habitual use of talcum powder products contaminated with fibrous talc, once the analysis of additional samples of talc is complete.

- I also reviewed the deposition and exhibits of Julie Pier, corporate representative for Imerys Talc America, Inc., who testified to numerous positive tests for asbestos and heavy metals between 1985 and 2002. (35).

- My review of monographs published by the International Agency for Research on Cancer (IARC) show that asbestos is a well-established carcinogen and unequivocally known to cause several cancers including mesothelioma of the lung, larynx, and ovarian cancer. (36). Overall, the International Agency for Research on Cancer Working Group classified asbestos compounds as "carcinogenic to humans" (Group 1) in 2012. (36, 37). IARC has also concluded that talc including asbestiform fibers grown in an asbestiform habit - commonly termed "fibrous talc" - is "carcinogenic to humans" (Group 1). (38).

- I also reviewed documents demonstrating talcum powder products may contain heavy metals such as chromium, nickel, and cobalt. (22). Asbestos, chromium, and nickel were all classified as a Group 1 carcinogens by IARC. (36) Cobalt is also present in talcum powder products and classified by IARC as a Group 2B carcinogen.

VII. SUMMARY OF OPINIONS.

1. **Statistical Significance**. There is a statistically significant increased risk of ovarian cancer with talcum powder products as demonstrated by most meta-analyses to date. (10, 39-42). Although a flawed analysis conducted limited to the use of talc dusted diaphragms and ovarian cancer conducted on behalf of the manufacturer reported an excess risk which was not

statistically significant, (13) it had several data extraction errors and was of lower methodological quality. (43). Several independent meta-analysis by academic researchers, some of which include individual participant data, (10) and the most recent meta-analysis reported a statistically significantly increased risk of ovarian cancer associated with perineal talc use, (42) rendering the previous findings of Huncharek et al obsolete. The studies of the highest rated methodologic quality as shown in **Table 1** which provides a methodologic grading of the quality of the included systematic reviews using the AMSTAR checklist have reported a statistically significantly increased risk of ovarian cancer associated with genital talc use. (10, 41, 42). See Section IX.IV for a summary of findings from epidemiological studies.

2. **Consistency and Replication**. These findings of a statistically significantly increased risk of ovarian cancer with talc use have been consistently replicated by several independent investigators in different population, and different settings across different data sources using different study designs. These slight differences in magnitude of risk reflect differences in inclusion or exclusion criteria and the accumulation of evidence over time. The meta-analysis of case-control studies has consistently shown a statistically significantly increased risk, whereas the meta-analysis of cohort studies has also shown an excess risk, (42) which failed to reach statistical significance, due to inadequate statistical power and low number of events; but the confidence intervals of results between the two study designs overlap providing evidence of consistency. The number of ovarian cancers in the case-control studies exceeds the number of ovarian cancers in the cohort studies by several fold. (42).

3. **Strength of Association**. The cumulative strength of association for the increased risk of ovarian cancer associated with talcum powder containing products is significant and ranges from 30 % to 60% %. The strength of association is similar to estimates of other established carcinogens (e.g., 24 % increased risk of lung cancers in non-smokers exposed to environmental tobacco smoke) (44), hormone replacement therapy and breast cancer (RR 1.33, 95% CI: 1.24-1.44) (45), particulate matter and lung cancer (PM2.5: RR 1.09, 95% CI: 1.04, 1.14 and PM10: 1.08, 95% CI: 1.00-1.17). (46). Beyond carcinogens, there are well established examples of causal associations in epidemiology, such as in the case of particulate matter and myocardial infarction, where the statistically significant excess risks are in the order of even less than a percent (carbon monoxide: 1.048, 95% CI: 1.026-1.070; nitrogen dioxide: 1.011, 95% CI, 1.006-1.016; sulfur dioxide: 1.010, 95% CI: 1.003-1.017; PM(10): 1.006, 95% CI: 1.002-1.009; and PM(2.5): 1.025, 95% CI: 1.015-1.036 and ozone: RR 1.003, 95% CI: 0.997-1.010; P = .36). (47).

4. **Exposure-Response Assessment.** The assessment of exposure–response or biological gradient is hindered by the difficulty in quantifying talcum powder use usually collected by

self-reported data (frequency, amount, and duration), timing and patterns of use (e.g., douching), and other individual factors (e.g., co-existence of inflammatory conditions such as endometriosis and or vaginal bleeding) resulting in differences in measurement of exposure across studies. As discussed in the dose-response summary of epidemiological studies below, some studies have measured the frequency of exposure, others the duration of exposure with few studies measuring the combined duration and frequency or intensity of exposure. (48). It is important to interpret the exposure-response data in the context of mechanistic studies which report that talc accelerates the development of ovarian cancer through alteration of the redox state in epithelial ovarian cancer cells, (49) and a monotonic dose-response curve may not accurately reflect this mechanism of development of ovarian cancer mediated via inflammation and alterations in redox states. Some epidemiologists have argued that it is difficult to know how dose-response should be modelled and it is unclear why nature would mandate a monotonic dose-response gradient. (50). Although it is difficult to know how to model the talc-ovarian cancer exposure-response assessment, it is possible that an agent which accelerates the development of cancer could account for threshold effects rather than monotonic dose-response effect. Despite these challenges, I address studies which have shown evidence of dose-response as measured by an increased risk with increased frequency, (48, 51-55) or increased duration, (52, 54, 56) or a combination of frequency and duration of exposure. (52, 57). Some studies have also shown evidence of increased risk with increased number of lifetime applications, (10, 48, 52) which may be a more accurate measure for long term exposure outcome association mediated via inflammation. The most updated meta-analysis reported an increased risk with >3600 lifetime applications compared to <3600 lifetime applications of perineal talc based on data from case-control studies. (42). A limited number of studies have shown no evidence of dose-response either with increased frequency or duration of exposure. (58-60).

5. **Retrograde Migration of Talc and Routes of Talc Exposure.** Talcum powder particles can migrate to the fallopian tubes and ovaries. (61-63). Talc and/or other constituents have been detected within the ovaries of women who report perineal talc use, (64) and found deeply embedded within ovarian tumors. (62, 65). Talc has also been reported in the lymph nodes which could occur through migration absorption or inhalation with transport through the lymphatic system. (66). Although an industry funded study performed by the Cosmetic, Toiletry, and Fragrance Association failed to detect translocation of "measurable quantities of talc" in unrelated monkey models, (67) the timing and techniques of assessment and intraspecies differences could not completely rule out migration of talc particles. Furthermore, supportive evidence for migration comes from the findings of a decreased risk of ovarian cancer with tubal

ligation and hysterectomy, (62) evidence of migration of other particles such as starch. (68). The FDA concluded that the "potential for particles to migrate from the perineum vagina to the peritoneal cavity is indisputable." (69). A secondary route of exposure is inhalation. (36, 70).

6. **Multiple Biological Mechanisms of Talc Induced Ovarian Cancer.** Although not an absolute requirement for demonstrating causality, there is strong evidence that talcum powder products can induce ovarian cancer through established biological mechanisms (Section X). (39, 49, 71, 72). Inflammation plays a leading role in ovarian cancer and talc has pro-inflammatory effects; it also induces alterations in redox potential and pro-oxidant effects. (49) In ovarian cells talc has been shown to increase proliferation, increase neoplastic transformation and increase reactive oxygen species in the ovarian cells. (71). Talc has also been shown to be mutagenic in human ovarian epithelial cells through increased activation of gene activating transcription factors. Finally, the presence of asbestos and other Group 1 carcinogens likely contributes to the carcinogenicity of talcum powder products, and provides biologic plausibility for the consistent and significant increased risk seen in the epidemiologic studies on Talc and Ovarian cancer.

VIII. METHODS FOR THE OVERVIEW OF SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES OF GENITAL TALC USE AND OVARIAN CANCER.

I conducted an overview of systematic reviews and meta-analysis of observational studies of genital talc use and ovarian cancer. I included systematic reviews regardless of the performance of quantitative synthesis as meta-analysis may occasionally not be performed for data from observational studies. To inform the causal question, I also evaluated additional studies which provided evidence on the causal question of whether talcum powder products induce ovarian cancer. I critically appraised the meta-analysis using the 11- item AMSTAR (Assessing the methodologic quality of Systematic Review) checklist for systematic reviews and meta-analysis. (12) The individual epidemiological studies were also evaluated and summarized for their key strengths and limitations.

VIII.I. Systematic search. I performed an initial systematic search of Scopus and PubMed with the following search terms on June 12, 2017:

Pubmed: ("talc"[MeSH Terms] OR "talc"[All Fields]) AND ("ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] AND "neoplasms"[All

Fields]) OR "ovarian neoplasms"[All Fields] OR ("ovarian"[All Fields] AND "cancer"[All Fields]) OR "ovarian cancer"[All Fields])

Scopus: (TITLE-ABS-KEY (talc) AND TITLE-ABS-KEY (ovarian AND cancer)

VIII.II Eligibility Criteria. I included and considered epidemiological studies, including case-control studies, cohort studies and systematic review and meta-analysis which reported on the association between talc and ovarian cancer. I searched the references of included studies and citing articles to find additional original articles. I also included in vitro, animal, and human epidemiologic studies that reported data that either support or refute the role of talc in the development of ovarian cancer. I excluded duplicate articles identified in the two databases, articles with no original data, narrative reviews, commentaries and opinion pieces , and citations not relevant to the present scenario. The title and abstracts of each manuscript were reviewed to identify potential studies for inclusion in this report. I also searched the reference of included studies to find relevant citing articles. New studies were identified after evaluating citing articles. I reviewed the full length of each of these manuscripts and provide a summary of their key findings below.

IX. RESULTS.

The results of the initial search yielded 273 citations. I included 9 studies in the section on overview of systematic reviews and meta-analysis. (10, 13, 39-42, 57, 73, 79). I also assessed the 29 case-control studies, (48, 51-60, 62, 66, 75-91) and 3 cohort studies (14, 17, 92-93). The list of excluded citations is shown. The difference in the citation count of included and excluded articles largely reflects excluded duplicate articles retrieved from the two databases. I also evaluated several studies (36, 37, 49, 64-68, 72, 94-109) which reported on the biological mechanisms that supported or refuted the causal association between talcum powder products and ovarian cancer.

IX.I. Overview of Systematic Reviews and Meta-analysis. Three meta-analysis were not preceded by a systematic search (57, 73, 79). There were 4 systematic reviews and meta-analysis which evaluated the link between perineal talc use and ovarian cancer (39-42) using summary data, while an individual participant data analyses pooled data from case-control studies in the Ovarian Cancer Consortium (10). Another systematic review and meta-analysis analysis conducted on behalf of the manufacturer only evaluated the use of cosmetic talc on

contraceptive diaphragms and ovarian cancer (13) and was not directly relevant to the causal question of genital talc use and the development of ovarian cancer, but was critically evaluated for strengths and weaknesses. The results of the methodologic assessment of each of these using the AMSTAR checklist is summarized in the Table 1. Two meta-analysis (13, 40) are of poor methodological quality. Regardless, the findings of older meta-analysis have been superseded given the publication of new meta-analysis. (41, 42).

1. In 1992, Harlow et al. combined crude odds ratios from their case-control study, discussed below with 5 pre-existing existing case-control studies (79) to evaluate the association between perineal talc exposure and ovarian cancer. The studies included 1106 cases and 1756 controls, with talc exposure reported among 50.7% of cases and 46.9% of controls. Using crude odds ratios from the individual studies, perineal exposure to talc was associated with a statistically significantly increased risk of ovarian cancer (OR 1.3, 95% CI: 1.1-1.6). Major limitations include the lack of a systematic search methodology.

2. A 1995, meta-analysis by Gross and Berg (39) was conducted on behalf of the manufacturer Johnson and Johnson. A search of PubMed issuing the terms "ovarian cancer" and "talc or cosmetic" identified 9 case-control studies and reported a statistically significant increased risk of ovarian cancer in both the crude odds ratio (1.27, 95% CI: 1.09-1.48) and adjusted odds ratio (1.31, 95% CI: 1.08-1.58). They also examined the odds ratio by tumor type and notes that all the analyses produced relative risks greater than 1 with confidence intervals that exceeded 1. Despite the statistically significantly increased risk seen in analyses, the authors concluded that the *"literature does not unequivocally support the hypothesis…. But [does] suggest the possibility of an increased risk of ovarian cancer due to perineal talc use."* The description of study procedures was incomplete, and the search strategy was limited. The study was supported in part by the manufacturer.

3. Cramer et al. 1999 combined crude odds ratio data from their case-control study with pre-existing case-control studies in a meta-analysis of 14 total case-control studies, (57) and reported a statistically significant OR of 1.36 (95% CI: 1.24-1.49). The tests for statistical heterogeneity were not significant (p=0.085). Limitations include the lack of a systematic search.

4. Huncharek, for his 2003 publication, conducted a meta-analysis of 16 studies including 11,933 subjects. (40). They searched MEDLARS, Embase and Cancer Lit databases using search term "talc exp ovarian neoplasms." They excluded studies on borderline tumors or those which did not report on types of perineal exposure (dusting vs sanitary napkins). The meta-analysis was conducted using adjusted measures of effect using the inverse variance method. It included 15 population-based and 1 hospital-based study and excluded the 1983 Hartge study. (76). The pooled analyses yielded a significantly increased risk of ovarian cancer (RR 1.33, 95% CI: 1.16-1.45) associated with the perineal use of talc without evidence of statistical heterogeneity. Seven studies reporting on the number of talc applications per month were evaluated where the highest risk category (RR 1.21, 95% CI: 1.00-1.45) and lowest risk category (RR 1.83, 95% CI: 1.55-2.15) reported an increased risk. In sensitivity analyses, hospital-based studies showed no statistically significant excess risk between talc use and ovarian cancer risk, i.e., RRs 1.19 (95% CI: 0.99-1.41) versus population-based studies which showed an increased risk (RR 1.38, 95% CI: 1.25-1.52), despite the proportion of controls using talc being similar across the two designs. The confidence intervals were overlapping suggesting that the findings were consistent. Recent updated meta-analysis discussed below report similar estimates from hospital and population based studies. (42). The RRs were relatively stable even after exclusion of the single cohort study or limiting the analysis to studies that controlled for body weight and BMI. The authors stated that the association between talc use and ovarian cancer could also be attributed to exposure misclassification among prevalent cases or side effects of treatment such as radiotherapy and chemotherapy which may predispose to talc use ("reverse causality"). Study limitations include the inability to conduct meaningful dose-response analysis because only nine of the 16 studies provided data on dose-response, with substantial differences in dose stratification levels among these studies.

5. Langseth reported on a meta-analysis of 20 case-control studies and one cohort study in 2008. The various case-control studies provided a significant excess risk (10 studies) and non-significant excess risk in 10 studies. (73). The prospective cohort study reported no association between cosmetic talc use and all types of ovarian cancer combined but showed evidence of an increase in serous tumors. The hospital-based case-control studies reported a pooled OR of 1.12 (95% CI: 0.92-1.36) and population-based case-controls studies reported a pooled OR of 1.40 (95% CI: 1.29-1.52). The combined OR from all case-control studies using the fixed effects model was 1.35 (95% CI: 1.26-1.46).

6. Terry et al conducted an individual participant pooled analysis of eight case-control studies was conducted by the investigators for the Ovarian Cancer Consortium. (10). Genital powder use was defined as any powder use (talc, cornstarch, deodorizing) applied directly or indirectly (with sanitary pads, tampons or underwear) to genital, perineal or rectal area. Criteria for exposure varied from ever use to one year or longer. Women who reported both genital and non-genital powder use were considered genital users. Cumulative exposure was calculated by multiplying months of use by frequency of use. Never users and women who reported non-genital powder use were considered as the reference group. Analyses were adjusted for potential confounders such as age, duration of contraceptive use, parity, tubal ligation history, BMI and race/ethnicity. Family history of breast and ovarian cancer was not included in the final model. Genital powder use was reported in 25% of controls and 31% of cases. The rates of genital powder use varied widely between studies ranging from 15-45% in the control group. Ever regular uses of genital powder reported a statistically significantly increased risk of ovarian cancer (OR 1.24, 95% CI: 1.15–1.33) compared to non-users. There was no evidence of heterogeneity in the studies regardless of the reference group ($P_{heterogeneity}$=0.61). Results were similar when the reference group included those with genital powder use and never users. Risk was elevated for various histologic subtypes of ovarian cancer including invasive serous (OR 1.20, 95% CI: 1.09–1.32), endometrioid (OR 1.22, 95% CI: 1.04–1.43), and clear cell (OR 1.24, 95% CI: 1.01–1.52) tumors, and for borderline serous tumors (OR 1.46, 95% CI: 1.24–1.72). There was an increased risk of all nonmucinous subtypes of epithelial ovarian cancer combined across quartiles of genital powder use compared with nonuse: (OR_{Q1} 1.18, 95% CI: 1.02–1.36; OR_{Q2} 1.22, 95% CI: 1.06–1.41; OR_{Q3} 1.22, 95% CI: 1.06–1.40; OR_{Q4} 1.37, 95% CI: 1.19–1.58). Although a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis (P_{trend} < 0.0001), no significant trend was seen when analyses were restricted to ever users (P=0.17). After excluding those with tubal ligation or hysterectomy, the results were similar. Restricting analysis to applications before tubal ligation made no substantive difference. There was an evidence of interaction by BMI, with the risk being higher for women with BMI < 30 kg/m^2 (OR 1.28, 95% CI: 1.17-1.39) than women with BMI ≥ 30 kg/m^2 (OR 1.14, 95% CI: 0.98-1.32; $P_{interaction}$=0.01). There was no evidence of interaction by tubal ligation, parity, endometriosis or post-menopausal status. The association was similar for women who used powder during varying time periods (1952-1961; 1962-1972; and after 1972). The strengths of this meta-analysis include the use of individual participant data, which allowed them to conduct dose-response analysis and analysis by histologic subtype. The lack of statistically significant evidence on non-

mucinous cancer could be attributed to the low number of users, or talc may not be relevant to these tumor types which have different biological mechanisms. The limitations include the definition of exposure as genital powder user varied from ever user, ever regular user to powder use for at least 6 months or at least 1 year in the studies.

7. Berge et al. 2018, a meta-analysis of 27 studies (41) (24 case-control studies and 3 cohort studies) was conducted according to the Preferred Item for Reporting of Systematic Reviews and Meta-Analysis Guidelines. (110). The authors searched multiple databases including Pubmed, Embase and Scopus. They examined the citations independently and in duplicate. They rated the studies using the New Castle Ottawa scale for study quality. They conducted meta-regression for duration (RR for every 10-year increase in duration) and frequency of genital talc use (RR for one time/week increase in frequency) for studies reporting at least three categories of duration or frequency after excluding the non-exposed category. Dose-response analysis was conducted using two methods. Study specific slopes were estimated from the natural logarithm of the risk estimates within each study; in a second step the slopes were pooled using a random-effects model. The study specific estimates were pooled in a single meta-analysis in the second method. Six of the case-control studies were hospital-based and the remainder were population-based. Most of the studies were conducted in North America and Europe. They reported a statistically significant increase in risk of developing ovarian cancer with talc use (adjusted RR 1.22, 95% CI: 1.13-1.30). A statistically significant risk was seen in the case-control studies (RR 1.26, 95% CI: 1.17-1.35), whereas the excess risk in the cohort studies did not reach statistical significance (RR 1.02, 95% CI: 0.85-1.20; $P_{heterogeneity} = 0.007$). There was no difference between results for borderline (RR 1.27, 95% CI: 1.09–1.44) and invasive ovarian cancer (RR 1.20; 95% CI: 1.08–1.31). There was a trend in RR with duration and frequency of genital talc use and suggestion of dose-response. There was a statistically significant risk for only serous carcinoma (RR 1.24, 95% CI: 1.15–1.34) and no other histologic subtypes ($P_{heterogeneity}$ between histologic types was 0.04). Use of talcum powder in the "early" period showed increased risk of ovarian cancer (RR 1.18, 95% CI: 0.99–1.37). The use in the "late" period was higher (RR 1.31, 95% CI: 1.03–1.61; P-value for test for heterogeneity between the groups of studies was 0.37), arguing against the hypothesis that a higher risk would be seen only among those with earlier exposure during time-periods in which talcum powder was reported to contain asbestos. The cut-off points varied between studies was variable between 1970 and 1980. Use of sanitary napkins or diaphragms was not associated with an increased risk of ovarian cancer (RR 1.00: 95% CI: 0.84–1.16, and RR 0.75, 95% CI: 0.63–0.88, respectively).

Stratified analysis based on the adjustment for confounders (use of oral contraceptives and hormone replacement therapy, socioeconomic status/ education, BMI) found no evidence of heterogeneity. Meta-regression using the two different approaches yielded similar results. Based on the two-step approach, a 10-year increase in genital talc use was associated with a RR of 0.97 (95% CI: 0.82–1.12; nine studies reporting on duration), whereas the RR for an increase of one application per week was 1.03 (95% CI: 0.82–1.25; five studies reporting on frequency). There was no evidence of publication bias on visual inspection of funnel plot and the Egger test (P=0.7), with the cumulative meta-analysis reporting stabilization RR of in the range of 1.20–1.25. Stratified analyses conducted did not suggest the possibility of residual confounding (i.e, higher adjusted estimates than unadjusted estimates).

There are some limitations to the analysis. While the role of selection and recall bias is a possibility, given higher estimates reported from recent studies, such biases should account for increase in recall for all histologic cancer subtypes and not just serous ovarian cancer. Importantly, the dose-response analyses analyzed duration and frequency separately and not the intensity of exposure (duration combined with frequency) or cumulative exposure to talc and the exclusion of the reference category from the dose-response curve diminished the power of the dose response analysis to detect any threshold effects.

8. Penninkilampi, et al. 2018 (42), the most recent and comprehensive meta-analysis which focused on studies with greater than 50 cases of ovarian cancer also reported on data from 26 case-control studies (13,421 cases and 19,314 controls) and 3 cohort studies (890 cases). The study was also conducted according to the PRISMA protocol and included a search of multiple databases (MEDLINE, PubMed, EMBASE, Cochrane Central Register of Controlled Trials) and LILACS. They also evaluated the quality of studies using the Newcastle Ottawa Scale. They also evaluated long term talc use in which OR were extracted for group with the longest duration of exposure compared to controls, if there was a minimum of 10 years of talc exposure. Lifetime applications within each study were divided into < 3600 lifetime applications (equivalent to less than 10 years) and >3600 applications or more than 10 years of exposure. The number of lifetime applications is a better marker of intensity of exposure compared to duration or frequency of exposure alone. They assessed publication bias using the failsafe method where the failsafe number is the number of studies missed to nullify the findings of meta-analysis.

This was a well-conducted analysis and some strengths and limitations are notable. They found all studies to be of reasonable quality and did not exclude studies based on study quality. None of the analyses in this review had statistically significant heterogeneity except for non-perineal application arguing for the consistency of estimates. Any perineal talc use was associated with an increased risk of ovarian cancer (OR 1.31, 95 % CI: 1.24-1.39). Greater than 3600 lifetime applications were more associated with ovarian cancer than lifetime applications of less than 3600, although risks were significantly elevated in both groups. While the case-control studies reported a statistically significantly increased risk of ovarian cancer (OR 1.35, 95% CI: 1.27-1.43), the cohort studies reported an increased risk which was not statistically significant (OR 1.06, 95 % CI: 0.90-1.25).

9. Meta-analysis on Talc-Dusted Diaphragms and Ovarian Cancer. Another meta-analysis of 9 case-control studies by Huncharek et al. (13) reported on exposure to talc dusted diaphragms and ovarian cancer. On one hand, the authors dismissed the "talc hypothesis" for potential carcinogenicity, but then argued that talc dusted diaphragms was a more "intuitive model" for testing whether talc exposure increased the risk of ovarian cancer without any biological evidence (or references) to support this intuition. They searched MEDLARS, Cancer Lit and Current Contents. They included 9 studies and the pooled analyses yielded an excess risk of ovarian cancer which was not statistically significant (RR 1.03, 95% CI: 0.80-1.33). Exclusion of the study in which exposure to dusted diaphragms was assumed rather than measured further elevated the OR, which was not statistically significant (OR 1.12, 95% CI: 0.84–1.48) similar to a non-significant elevation in OR after the exclusion of the studies not published as full research articles.

This meta-analysis was flawed for several reasons. <u>The most important limitation was its exclusive focus on talc powder dusted diaphragms as the route of exposure which could not inherently address the causal question of whether genital talcum powder dusting is associated with increased risk of ovarian cancer.</u> As a result of this narrow hypothesis, they excluded several available studies that reported a statistically significant excess risk of ovarian cancer with perineal talc use. Several methodological flaws include the exclusion of the lowest category of exposure for some studies, (51) data extractions errors for others (56), and inclusion of ineligible studies that did not disaggregate data between talc and cornstarch users. (77) The study was by Johnson & Johnson and Luzenac America and was of poorer methodological quality than those conducted by their academic counterparts (43). As a result of these serious methodological

flaws, and the publication of several newer, higher quality meta-analysis with updated data, (10, 41, 42) the findings of this study have been superseded.

It is important to note here that while the AMSTAR checklist evaluates the methodologic quality of systematic reviews, several studies shown below were published prior to the publication of the AMSTAR checklist.

IX.II. Case-Control Summaries.

1. More than three decades ago Cramer et al. (75) evaluated 215 white women diagnosed with epithelial ovarian cancer identified through 12 hospitals in the greater Boston area. They were randomly matched by age, race and residence to 215 population-based controls. Surgical specimens were reviewed to confirm and classify tumors by histologic type. Talc exposure was determined through in person interviews. Multivariable logistic regression was used to estimate the Relative Risk. Ninety-two (42.8%) cases regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 (28.4%) controls.

Adjusted for parity and menopausal status, this difference yielded a RR of 1.92 (95% CI: 1.27-2.89) for ovarian cancer associated with talc exposure. Women who had regularly engaged in both practices had an adjusted RR of 3.28 (95 % CI: 1.68-6.42; $P < 0.001$) compared to women with neither exposure. After adjusting for religion, marital status, educational levels, ponderal index, age at menarche, parity, oral contraceptive or menopausal hormone use and smoking the RR was attenuated but remained statistically significant (RR 1.61, 95% CI: 1.04-2.49). The limitations of the study include the potential for selection bias in controls because of high rates of non-participation, although RR remained statistically significantly elevated even though the analysis was restricted to 121 cases matched with controls without a referral. Since approximately 50% of ovarian cancer cases in the Boston area was sampled, any potential for pervasive selection bias of cases was minimal. Other potential limitations include the adjustment for only a limited set of confounders such as parity and menopausal status.

2. Hartge et al. 1983 (76) conducted a hospital-based case-control study of women with pathologically confirmed primary epithelial ovarian cancers matched to equal number of women for conditions other than gynecologic, psychiatric, or malignant diseases or pregnancy in the same hospitals in Washington, DC. Controls were frequency matched for age, race and hospital. Exposure to talc was ascertained through questions about reproductive and sexual history, medical history, drug use, and other exposures. The questions for talc use were added after the study began yielding 135 cases and 171 controls.

Among the women users of talc in sanitary napkins, underwear, or the genital area there was an excess risk of ovarian cancer (unadjusted RR 2.5, 95 % CI: 0.7-10.0) which was not statistically significant due to small sample size (n= 7 cases and 3 controls). The limitations to the study include the limited number of cases and controls reporting genital use of talc (n=10) and publication as a letter to the editor which may or may not undergo peer review depending on editorial practices at the journal. They did not report adjusted results of ovarian cancer after perineal exposure to talc. Another limitation is the potential for recall bias; however, this was likely minimal given similar reporting of douching practices in cases and controls.

3. In 1988, Whittemore et al. (58) evaluated 188 pre-menopausal and postmenopausal women between the ages of 18 and 74 with primary epithelial ovarian cancer in Santa Clara County hospitals or at the University of California, San Francisco Medical Center. The diagnoses were subsequently histologically verified. One group of controls was selected from the hospital (n=280); and a second group was selected from the population using random digit dialing (n=259). Exposure to talcum powder products was determined through a structured in-person interview at home where subjects were asked about whether they had used talcum powder products on the perineum, sanitary pads and/or diaphragms. Data was recorded by type (perineum, sanitary pads, diaphragm or some combination thereof), and duration of use.

Population cases were more likely to be younger and more likely to be premenopausal than cases and hospital-based controls. Approximately 52% of cases reported talc use compared to 46% controls (RR 1.40, p=0.6). After adjusting for parity and oral contraceptive use, perineal use of talc was associated with an excess risk of ovarian cancer that was not statistically significant (RR 1.45, 95% CI: 0.812.60). Women who used talc an average of 1-20 times per month reported an excess risk in comparison to those who used it less frequently which was not statistically significant (RR 1.27, p=0.29). The risk among users of more than 20 times per month was 1.45 times greater than non-users, but the findings were not statistically significant (p=0.09). The overall increased risk in overall applications per month was 1.30 (p=0.19). Although the data showed a *trend* of increasing risk with increasing frequency of perineal exposure, the trends were not statistically significant and there was no trend with increasing duration of exposure. The risk of ovarian cancer with talc use between one and nine years was 1.6 times the risk of those with a shorter duration (95% CI: 1.00-2.57; p=0.05), and the risk among those with more than 10 years of exposure was 1.11 higher than that of non-users (95% CI: 0.74-1.65; p=0.61).

The limitations of the study are the inability to interview cases and the choice of two controls. Some amount of non-differential misclassification of exposure may bias findings towards null. The dose-response analysis was limited by the inability to determine the combined effect of frequency and duration of exposure. The study reported a statistically increased risk of ovarian cancer with coffee consumption and a non-significant reduction in risk with smoking. Subsequent meta-analysis (111) or Mendelian randomization (112) studies have confirmed that there is no association between coffee consumption and ovarian cancer, whereas smoking has a heterogenous relationship to ovarian cancer which varies by histologic subtypes. (112) The reports of such additional spurious associations suggest an element of measurement error in their database.

4. Harlow et al. 1989 (77) conducted a population-based case-control study which included 116 females 20-79 years old h *serous and mucinous borderline ovarian tumors* identified using International Classification of Disease (ICD)-9 codes from the cancer registries of three western urban counties in Washington State. An independent pathology review confirmed diagnosis for 73% of tumors with 94% agreement, so the additional 33 cases were included. A sample of 158 controls of white women was identified through random digit dialing. Women with bilateral oophorectomy were excluded from the analysis. Any exposure to talc including any perineal exposure to powder, method of use, type of powder use (cornstarch, baby powder, talc, deodorizing powder), and combinations of method and type was ascertained through in-person interviews.

The study reported no statistically significant increased risk of ovarian cancer with perineal use of dusting powders (RR 1.1, 95% CI: 0.7-2.1). When looking at unspecified talc adjusted for the same factors, the RR was 1.0 (95% CI: 0.4-2.4). However, women who reported any use of talc containing powder on sanitary napkins showed an excess risk which was not statistically significant due to limited statistical power (RR 2.2, 95% CI: 0.8-19.8). However, among the sample of women who used deodorizing powders alone or in combination with talc, the risk of ovarian cancer was RR 2.8 (95% CI: 1.1-11.7) attributed to the potential exposure to asbestos. The limitations to the study include the potential for selection bias since 30% of cases and controls did not participate, although their characteristics were like the included participants which may have limited any impact. It is also possible that these findings are limited to borderline rather than malignant ovarian cancers.

5. In 1989, Booth et al. (51) conducted a population-based case-control study of 280 cases of ovarian cancer in women under 65 years of age from 13 hospitals in London and two in

Oxford. 451 controls were selected from other hospitals as enough age-matched controls were unavailable. The study included both pre- and post-menopausal women. Ovarian cancer was determined through hospital diagnoses with pathological specimens being histologically classified. Serous tumors were most prevalent, though mucinous, endometroid and clear cell carcinoma was included. Information regarding talc exposure was obtained through a questionnaire and frequency of talc use was reported as never, rarely, monthly, weekly, or daily talc use.

After adjusting for age and social class (based on occupation of the husband for married women, and their own occupation for women who were not married) talc users reporting use more than once a week had a higher risk compared to never users. (RR 2.0, 95 % CI: 1.3-3.4). Those who reported daily use also had a non-significantly higher risk (RR 1.3, 95% CI: 0.8-1.9). There was some amount of missing data (8% of cases and 4% of controls), and no consistent trend of increasing risk with increasing frequency of use. However, data was not available on the duration of talc exposure to conduct meaningful dose-response analysis.

6. In 1992, Harlow et al. (79) included 235 cases of white women between the ages of 18 and 76 who had been diagnosed with ovarian cancer at one of 10 hospitals in the Boston metropolitan area. Controls were randomly selected from the town books; annual publication lists and address lists within 2 years of the age of case as potential controls. Cancer was confirmed through an independent pathology review. Talc exposure was determined through in-person interviews. Talc exposure from infancy with diapering, or use on other parts of the body, was not included. Talc use in other parts of body was considered unexposed. Talc use was reported as any genital application, type of application (sanitary napkin/underwear, via partner or application to diaphragm, via dusting to perineum), number of applications per month, years of use, age at first use, years since last use, whether use was before or after 1960, brand of application, estimated total lifetime applications, estimated applications excluding use after hysterectomy or tubal ligation, and estimated applications excluding use after hysterectomy or tubal ligation and use during nonovulatory months. The Chi square test for change in linear trend based on change in deviance in models.

Most participants reported use of baby powder. Perineal talc use was associated with an increased risk for ovarian cancer (OR 1.5, 95% CI: 1.0-2.1) when adjusted for parity, education, marital status, religion, use of sanitary napkins, douching, age, and weight. Perineal use of talc via dusting powder to perineum was associated with a significantly increased risk of ovarian cancer OR 1.7 (95% CI: 1.1-2.7), whereas use by sanitary napkins, underwear, use via

diaphragms was not associated with a significantly increased risk. Adjusted risk was highest for endometrioid tumors (OR 2.8, 95% CI: 1.2-6.4) and borderline tumors. A greater proportion of women with endometroid tumors reported more than 10,000 lifetime applications of talc during ovulatory cycles while having an intact genital tract compared to other histologic types (34 % vs 16%, respectively). The risk of cancer increased significantly with increased frequency of applications per month using a linear test trend as a continuous variable. The risk was highest among the women who applied talc once daily relative to non-users. Women who applied talc for more than 10 years were at 60% greater risk for ovarian cancer relative to non-users. An 80% excess risk was associated with an estimated exposure of more than 10,000 applications. The association between talc and ovarian cancer was greater than in talc products before 1960. Restricting the analysis to exposure during ovulatory months, women with intact genital tract and more than 10,000 applications during ovulatory cycles had a threefold increase in risk of ovarian cancer. Limitations included the high rates of non-response (n=31% cases and 19% of controls) and failure to adjust for family history of ovarian cancer and oral contraceptive use.

7. Chen et al. 1992 (78) evaluated 112 cases of ovarian cancer in Beijing China. The diagnosis was confirmed by laparotomy and pathological examination. Serous cancer accounted for 51% of cases, mucinous for 19%, and miscellaneous epithelial for 30% of cases. Two controls were matched for each case using random selection from the same street, office, or township. A comprehensive questionnaire was administered through face-to-face interviews and collected information about menstrual, obstetric, marital, medical, familial, and dietary histories with reference to events 3 years or more prior to diagnosis. A total of 224 controls were selected. Talc exposure was measured through a yes or no metric, for exposure occurring 3 or years prior to date of diagnosis or equivalent date in controls. Logistic regression was conducted to estimate relative risk.

The mean age of participants was 48.5 and 49 years among cases and controls respectively. After adjusting for education and parity, there was an excess risk of ovarian cancer associated with a history of long-term (>3 months) application of dusting powder to the lower abdomen and perineum (RR 3.9, 95% CI: 0.9-10.6) which was not statistically significant due to limited statistical power (n=7 cases and 5 controls reporting powder use). The limitations of the study include the small sample size, loss to follow up and death, the inability to fully ascertain all cases of ovarian cancer and the exclusion of controls with other health problems. Although the applicability of these findings from a Chinese population to a US population is limited, the

findings of an increased risk in different parts of the world provide evidence in support of an increased risk of ovarian cancer with dusting powder use.

8. In 1992 Rosenblatt et al. (80) conducted a hospital-based case-control study of the association between genital and respiratory talc exposure and the development of epithelial ovarian cancer at the Johns Hopkins Hospital. Among 140 diagnosed cases of epithelial ovarian cancer, approximately 108 were successfully interviewed. Seventy-seven pathologically-confirmed incident cases diagnosed within 6 months of admission were matched to age-race matched controls (n=46). Exposure was ascertained using a structured questionnaire administered at home and in the hospital. Conditional logistic regression was used to obtain strength of the association.

Although genital powder use was not associated with an increased risk of ovarian cancer, statistically significant increased risk was observed for exposure to talc on sanitary napkins (OR 4.79, 95% CI: 1.29-17.79) after adjusting for confounders such as obesity, socioeconomic status, religion, reproductive status and oral contraceptive use, with a smaller risk after genital bath exposure (RR 1.7, 95% CI: 0.7-3.9). An excess risk of borderline significance was seen for exposure of ≥ 37.4 years (RR 2.4, 95% CI: 1.0-5.8). The limitations include the small sample size, lack of data on frequency of talc use, and the limited generalizability of the findings from one hospital. The control group also reported a very high rate of talc use (90%) which may have limited the ability to detect any differences.

9. In 1993, Tzonou et al. (81) reported on a hospital-based study of 189 women under 75 years of age with histopathologically confirmed ovarian cancer in Athens, Greece compared with 200 hospital visitor controls in two hospitals. Control patients were those hospitalized in the same ward as cancer cases. Talc exposure was determined by asking participants to report talc use (over an extended period before the onset of illness for cases and for a comparable period among controls) among other characteristics, through interviews in the hospital. Talc use was reported as a yes/no metric. Estimates were adjusted for age, years of schooling, weight before onset of the disease, age at menarche, menopausal status and age at menopause, parity and age at first birth, tobacco smoking, coffee drinking, consumption of alcoholic beverages, hair dyeing and mutual (analgesics-tranquilizers/hypnotics) tranquilizers.

An exceedingly small number of cases (n=6) and controls (n=7) reported perineal use of a talc. There was no statistically significant increased risk of ovarian cancer associated with perineal application of talc (RR 1.05; 95% CI: 0.28 to 3.98). The limitations of the study include the low

proportion of talc exposure, which was ascertained in only approximately 3% of cases and controls.

10. In 1995, Purdie et al. (82) evaluated 824 histologically confirmed cases of epithelial ovarian cancer and 860 controls from gynecological oncology treatment centers in the three most populous Australian states. Controls were selected from electoral rolls in Australia where electoral participation is mandatory using a random procedure to match the age distribution of cases. Talc exposure was determined through face-to-face interviews conducted by trained interviewers using a standard questionnaire.

After adjusting for parity, there was a statistically significant increase risk of ovarian cancer reported with talc use on the abdomen or perineum (OR 1.27, 95% CI: 1.04-1.54). The limitations include high non-response rates in controls which may differ from the source population, but the age distribution of controls was like non-responders suggesting minimal response bias by age. There is also the possibility of bias in the selection of cases. They only adjusted for a limited set of confounders. Some misclassification of outcome is also possible given borderline and malignant cases were lumped together, although no differences were found when results were analyzed separately. Recall and interviewer bias was minimized by trained interviewers who administered standardized questionnaires.

11. In 1996 Shushan et al. (83) reported on findings from a study of two hundred living cases aged 36-64 years with history confirmed diagnosis of primary invasive or borderline invasive ovarian cancer in the Israel Cancer registry. There were 408 women from the same area selected by random digit dialing. Both were interviewed using standardized questionnaires.

A larger proportion of cases than controls reported using moderate to a large amount of talc (10.5% vs 5.6%; P=0.04) compared to never users or seldom users, a difference which was statistically significant. Limitations include high refusal rate for cases (30%), the low rates of talc exposure among controls and limited adjustment for confounders. (14)

12. In 1997, Cook et al. (84) reported on 329 white women between the ages of 20-79 diagnosed with epithelial and borderline ovarian cancer identified through the Cancer Surveillance System of Western Washington. Women were randomly selected as controls using random digit dialing from a larger pool of women for cancer studies. Genital powder exposure was collected through structured in person interviews and reported as any lifetime powder application, method of use (perineal dusting only, diaphragm only, sanitary napkin only, or genital deodorant spray only). Additional exposure information included cumulative

lifetime days of use for dusting and similar metrics for other methods of use. Genital powder use was also separated into use of talcum powder, baby powder, cornstarch, deodorizing powder, bath/body powder, or unspecified powder. Analysis was presented by age because adjustment for other confounders such as income, marital status, body mass index, oral contraceptive or parity did not change results.

Genital powder exposure was more common among cases (50.8%) than controls (39.3%). After adjusting for age, any use of genital powder was associated with a statistically significant increased of ovarian cancer (RR 1.5, 95% CI: 1.1-2.0) compared to non-use, although there was no clear pattern of increasing risk after increasing duration of use. After adjusting for age, exclusive use of perineal dusting was also associated with a statistically significant increased risk of ovarian cancer (RR 1.8, 95% CI: 1.2-2.9), whereas the risks for use via other routes of exposure (e.g. diaphragms, powder) were not significant. There was a statistically significant increased risk of serous tumors associated with any genital powder application (RR 1.7, 95% CI: 1.1-2.5), but not for the smaller number of mucinous or endometroid tumors. Limitations include low participation rates (64.3% for cases, 68% for controls), the potential for recall bias, and confounding by family history of ovarian cancer in a study where more than 50% of controls were less than 45 years of age.

13. In 1997, Chang et al. (56) conducted a population-based case study of cases of borderline and invasive histologically confirmed ovarian cancer among participants aged 35 to 79 years from Canada. Talc exposure was determined through a questionnaire conducted during an in-home in person interview to detail medical and reproductive histories. Powder use was reported as talc, cornstarch, or a mixture. Information was provided for type of exposure, number of uses per month, years of use, years of use pre- and post-1970, and well as years of use before and after a tubal ligation or hysterectomy. They adjusted for age, years of oral contraceptive use, number of full-term pregnancies, duration of breastfeeding per pregnancy, tubal ligation, hysterectomy, and having a mother or sister with breast or ovarian cancer.

Talc exposure was reported in 44% of cases and 35.6% of controls. After adjusting for confounders there was a statistically significantly increased risk of ovarian cancer associated any talc exposure via sanitary napkins, direct application to the perineum or both (OR 1.42, 95% CI: 1.08-1.86). The dose-response analysis showed a borderline-significant association was detected between duration of after-bath talc exposure and risk (OR 1.09, 95% CI: 0.98-1.21, per 10 years of exposure), without any significant association between frequency of exposure and

risk. Although risk was elevated for both invasive and borderline carcinomas, it was statistically significant only for invasive carcinoma. The limitations of the study include the potential for recall bias and the high rates of non-response (28.7% for cases and 35.5% for controls)

14. Green et al. 1997 (62) conducted a population based case-control study of 824 women aged 18-79 with histologically confirmed ovarian cancer compared to 824 controls. The methods and limitations were similar to the study by Purdie et al. (82). The prevalence of talc use was approximately 40% in the control use. Perineal talc was significantly associated with ovarian cancer (RR 1.3, 95% CI: 1.1-1.6), without any effect of longer duration of talc use. Compared to women who had neither used talc nor had sterilization, the risk was highest among talc users without surgery like the findings by Whittemore et al. (58). There is the potential for recall bias, and the quantity of talc use was unknown.

15. In 1998, Godard et al. (85) examined 170 French-Canadian women with a histologic diagnosis of ovarian cancer from 2 large Montreal teaching hospitals. Cancer diagnoses were histologically confirmed, and pathology reports were reviewed for tumor classification. 170 population-based controls were identified using modified random digit dialing to match the age distribution of cases. Talc exposure was obtained through a 57-item questionnaire. 70% of interviews were conducted in person in clinics and 30% were conducted via phone. Talc use was reported through an ever/never metric for perineal use.

Only 10.6% of cases and 4.7% of controls reported talc use. As a result, perineal talc use was associated with an increased risk for ovarian cancer which was not statistically significant (RR 2.49, 95% CI: 0.94-6.58; P = .066) because of limited statistical power. Similar patterns of excess risk which did not reach statistical significance were seen in both the comparisons for sporadic and familial cases and controls. The limitations of the study include a modest non-response rates among cases (13%) and controls (10.7%).

16. In 1999, Cramer et al. (57) evaluated 563 ovarian cases identified through tumor boards and statewide cancer registries in Massachusetts or New Hampshire in a population-based control study. Pathology reports were reviewed, and slides were sought in any case where there was a discrepancy between histologic description and final diagnosis. Controls were selected from the population using random digit dialing with a response rate of 72% among eligible controls. Talc exposure was obtained through questionnaires in which potential controls and cases were blinded. Specific hypothesis regarding talc use were not discussed. Exposure was assessed prior to 1 year before date of diagnosis or date of interview for

controls. Talc use in the genital or rectal area, on sanitary napkins and on underwear was considered as exposure whereas non-use and non-genital use was considered as unexposed. Exposure from condoms and diaphragms was not assessed.

Genital talc exposure was reported in 27% of cases and 18.2% of controls and the average duration of talc use exceeded more than 20 years in cases and controls. There was a statistically significantly increased relative risk of ovarian cancer with genital talc exposure 1.60 (95% CI: 1.18-2.15) after adjusting for age, study center, tubal ligation, BMI, parity, or primary relative with breast or ovarian cancer. The highest risk was seen among women whose age at first use was between 20 and 25 (RR 1.87, 95% CI: 1.03-3.39) those who have used talc for less than 20 years (RR 1.86, 95% CI: 1.16-3.00), those whose total applications is less than 3000 (1.84, 95% CI: 1.12-3.03), women who used talc when nulliparous (RR 2.80, 95% CI: 0.64-12.20), and those with serous invasive tumors (RR 1.70, 95% CI: 1.22-2.39). Only one case and 3 controls reported primarily using cornstarch, these numbers are likely accurate for talc use, despite the potential for including other kinds of powders. There was little evidence of effect by confounders such as age, oral contraceptive use and parity. Linear trends were significant in models that included women who were not exposed without any clear trend in duration or intensity of exposure in models that excluded women who were not exposed. Analysis of dose-response censured after closure of female tract or non-ovulatory cycles, and models showed a trend this was statistically significant only after inclusion of non-genitally exposed categories (P_{trend}=0.022).

Potential limitations include the potential for recall bias, although this is likely to be minimal and more likely to occur for short term exposures rather than long term exposures. The evidence for substantial degree of recall bias is refuted by the findings that there is no evidence of higher proportion of perineal talc exposure reported among cases in more recent compared to older studies to suggest stimulated reporting, no evidence of significant excess of non-genital talc exposure among cases, and the excess is limited to invasive serous carcinoma,(84) rather than all types of ovarian cancer or endometrial carcinoma.

17. In 1999, Wong et al. (86) reported-on a hospital-based study of 499 patients with epithelial ovarian cancer and 775 age-matched controls with non-gynecologic cancer diagnoses. Cancer diagnoses were confirmed in the cancer registry. Exposure was ascertained through self-administered questionnaire in which approximately 15% of participants did not respond to questions about talc use or its frequency.

Talc use was reported by 47.8% of cases and 44.9% of controls. Genital talc use was reported by 34% of cases and 32.2% of cases. The mean duration of talc use was 22 years in controls and 21 years in the study population. After adjusting for age at diagnosis, parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, history of tubal ligation, and previous hysterectomy there was no statistically significant increased risk of ovarian cancer among ever users of talc (OR 0.92, 95% CI: 0.24-3.62). There was no significant association between duration of use and development of ovarian cancer even after prolonged exposure of more than 20 years. However, when evaluating genital talc use via histologic subtypes of cancer, all ORs were above 1 (except for undifferentiated carcinoma) but were not statistically significant. Similarly, those who had no history of genital tract interruption the ORs were elevated but not statistically significant. However, the study was limited by the non-response rate and the choice of a controls with malignancies. (113). Additionally, data on exposure were reported on a self-administered questionnaire rather than administered by interviewers. The results could not rule out the effect of talc exposure via condom use and data was not available on the frequency of talc use.

18. Ness et al. (87) conducted a population-based control study. Cases (20-69) years of age with recent diagnosis of ovarian cancer (n=) were compared with community-based controls 65 years or younger through random digit dialing. Controls were age-matched as well as matched by last 3 digits of the phone number. Approximately 72% of controls were selected. As a part of detailed interviews with calendars women were asked about their reproductive history including talc use. The question was, “As an adult and prior to [reference date] did you ever use talc, baby or deodorizing powder, at least once per month for 6 or more months on your: 1) feet, arms, or breasts, but not the genital or rectal areas? 2) genital or rectal area? 3) on your sanitary napkins? 4) on your underwear? 5) on your diaphragm or cervical cap?” They were then asked whether they had a male sexual partner(s) for more than a year who regularly used such products on his genital area or underwear. The duration of use of talc for each of these modes of use was also queried. The estimates were analyzed using conditional logistic regression after adjusting for age and gravidity (each as continuous variables), race (white/black/other), history of ovarian cancer in any first degree relative (yes/no), oral contraceptive use (yes/no), tubal ligation (yes/no), hysterectomy (yes/no), and breast-feeding (yes/no).

Talc use was reported in 53.2 % of controls. Compared to never talc use, talc use on all parts of the body (OR 1.4, 95% CI 1.1-1.6), genital/rectal (OR 1.5, 95% CI 1.1-2.0) on sanitary napkins

OR 1.6, 95% CI 0 1.1- 2.3) and underwear OR 1.7, 95% CI. 1.2-2.4) was associated with a statistically significantly increased risk of ovarian cancer after adjusting for confounders. However, talc use on diaphragms (OR 0.6, 95% CI 0.3-1.2) or by male partner (OR 1.0, 95% CI 0.7 to 1.4) was associated with an increased risk which was not statistically significant. Although duration of talc use did not show a pattern of increased risk with increased risk with duration of exposure, the OR for each categories (> 1 year, 1-4 years, 5- 9 years and > 10 years) were elevated and were statistically significant for 1-4 years. Tubal ligation and hysterectomy decreased ovarian cancer risk. Limitations to the study include the low response rates among cases and controls due to exclusion of prevalent ovarian cancer. Recall bias while always a concern was less likely to be a concern given that risk factors overall did not increase risk but were limited to those linked to inflammation.

19. In 2004, Mills et al. (59) conducted a population-based case-control study of 256 women with histologically confirmed incident epithelial ovarian cancer from 22 counties in Central California. They also selected 1122 controls who were residents of that area who had one intact ovary and no history of ovarian cancer. Talc exposure was determined through phone interviews conducted by trained interviewers. Talcum powder use in the genial area was reported as an ever/never metric, as well as by frequency, duration, and cumulative use. The final parsimonious model adjusted for age, race, duration of oral contraceptive use and breast feeding.

The rates of talc use in controls was 37.1 % and higher among white non-Hispanics. Controls were more likely to have been outside the US. Most of talc exposed cases and controls were non-white. There was a statistically significant risk of ovarian cancer associated with genital talcum powder use (OR 1.37, 95% CI: 1.02-1.85) after adjusting or age, race, duration of oral contraceptive use, and breast feeding. Although increasing frequency of use showed a 74% increased risk among women who used talcum powder more than 4-7 times per week (P_{trend}= 0.015), this risk was not monotonic because risk the decreased between second (rarely to several times per month) and third categories (1 to 3 times per week). Duration of use also showed increasing risk and peaking between 4-12 years of use and declining thereafter (P_{trend} =0.045). Cumulative exposure increased in the second and third quartiles of exposure but declined among the highest quartile of users (P_{trend}=0.051). The risk was highest among those who had stopped using talcum powder in the last 1-2 years compared to those in the more distant past. The risks were primarily elevated for serous and mucinous tumors. Risk was higher among those reporting use after 1975 which may be related to the recency of use, and those after age 20. Limitations of the study include a low response fraction which was only

40% for eligible cases and 57% for eligible cases, and high rates of non-participation- 34.2% among cases and 29.3% among controls. The dose-response analysis did not exclude exposure during non-ovulatory periods or after gynecologic surgery which may have diluted the relative risk estimates. However, strengths include the ability to rule out prevalent cases by examining incident cases alone.

20. In 2004, Langseth et al. (88) conducted a case-control study of pulp and paper workers from different mills in Norway. Only one of these mills reported use of fibrous talc. They included 46 cases and reviewed histological records for each case. Most of the cases were invasive tumors. Four controls free of ovarian cancer and having intact ovaries were matched by birth year +/- 2 years and were drawn by incidence density sampling. A total 179 controls were available for analysis. Talc exposure was determined through personal interviews which took place in mill offices, at home, at a medical institution, or by phone. Talc exposure was reported environmentally and as use by personal hygiene (diapers, sanitary napkins, non-genital area or husbands use in genital area)

Talc exposure was reported among 50% of cases and 48% of controls. After adjusting for number of children, breastfeeding, age at birth of first and last child, age at menarche, age at menopause, smoking, and family history the use of talc use by personal hygiene was associated with an excess risk of ovarian cancer OR 1.15 (95% CI: 0.41-3.21), which was not statistically significant. The study has significant limitations. The sample size of the study was low with limited statistical power to detect a two-fold increased risk with a probability of only 53 % and response rate for interviews were low -76.1% for cases and 65.7% for controls. The inclusions of non-genital or husband's use in genital area among the exposed category diluted the estimates of relative risk for ovarian cancer associated with talc exposure. More information on cases was collected from relatives than controls because 71.5 of cases were deceased compared to only 28.6% of controls. The rates of missing data on talc use was high, because it was obtained from proxy respondents introducing an element of uncertainty in the estimates for relative risk of ovarian cancer associated with talc use.

21. In 2008, Merritt et al. (89) reported on a population-based study of 1,576 women with epithelial ovarian cancer as part of the Australian Ovarian Cancer Study. Pathology reports and diagnostic slides were reviewed for a sample of 87 women with 97% agreement with original abstracted data. Cases were confirmed by histopathology. 1509 controls were selected from the electoral rolls and were matched by age and residence. Talc exposure was identified through a comprehensive health and lifestyle questionnaire. Talc use was reported as

ever/never for perineal use (powder or talc in the genital area or on underwear or on sanitary napkins), years of use prior to surgery, use post-surgery, and use stratified by age at diagnosis. All analyses were conducted for talc use while the reproductive tract was patent and exposure occurring 12 months prior to the diagnosis of cases and similar period in controls was excluded.

The rate of talc use was 43% among controls and 46% among cases. When adjusted for age, education, parity, and oral contraceptive use of talc in the perineal region among women with patent tubes there was a statistically increased risk of ovarian cancer (OR 1.17, 95% CI: 1.01-1.36) with the highest risk reported for serous tumors (OR 1.21, 95% CI: 1.03-1.44). The tests for trends for duration of use were of borderline statistical significance for all cancers and serous subgroup (P_{trend} =0.02 for both). No significant associations between number of years used pre- or post-surgery and significantly elevated risks for overall cancer and serous ovarian cancer were seen in women both above 70 years of age, and below 50 years of age suggesting that timing of talc exposure (before or after 1976) did not affect results. There was no association between PID and the risk of ovarian cancer or the protective effect of NSAIDs. Limitations include low response rates and the lack of data on the frequency of exposure.

22. In 2008 Gates et al. (55) conducted a nested case-control study as part of the New England Case-Control study and the Nurses' Health Study (NHS). Further cohort analysis from the NHS are presented in the section on cohort studies below. **Section IX.III.I** Ovarian cancer diagnoses were confirmed by the researchers. They included 1385 cases and 1802 controls. 76.7 % of cases were incident with respect to the timing of DNA collection in the NHS. Exposure was accessed through a questionnaire that asked questions related to use of talcum powder. The NECC questionnaires included questions about regular use of talcum, baby or deodorizing powder as an adult. Specific questions asked about type of use (as a dusting powder to the genital area, sanitary napkins, underwear, or non-genital areas), frequency of use, age at first use, number of years used, and brand of powder used. The 1982 NHS questionnaire requested information on whether the participant had ever commonly applied talcum, baby, or deodorizing powder to the perineal area (no, <once/week, 1-6 times/week, or daily) or to sanitary napkins (yes/no). The study defined regular genital talc use as application of powder to the genital/perineal region at least once per week. We also created a categorical variable for frequency of talc use, using the categories from the NHS questionnaire.

Most of the participants were white. Regular genital talc was reported among 56 cases and 44 controls, and daily genital talc use reported among 35 cases and 25 controls, respectively. There was a statistically significant increased risk of total epithelial ovarian cancer (RR 1.36, 95% CI: 1.14-1.63; P<0.001) and of serous invasive subtype (RR 1.60, 95% CI: 1.26-2.02) associated with regular use of talc when adjusted for age, study center, duration of oral contraceptive use, parity, tubal ligation, BMI, and duration of hormone use. The New England Case-control study had a higher RR associated with genital talc use than the Nurses' Health which had a smaller sample size. There was a statistically significant trend between increasing frequency of talc use and risk of both total and serous invasive ovarian cancer in the pooled analyses (P *trend* < 0.001 for both total and serous invasive ovarian cancer). The association between talc and ovarian cancer was stronger among women with the glutathione S-transferase M1 (GSTM1) null genotype (P interaction = 0.03), particularly in combination with the GSTM1 present genotype alone (P interaction = 0.03) in two independent study populations. The strengths of the study include robust findings from two independent study populations. Although talc exposure was only measured in the 1982 NHS questionnaire when participants were between 36 to 61 years of age, the number of users who began talc use after this is likely small as shown by the fact that more than 95% of controls with regular talc in the NECC reported talc use before age 35. The consistent findings from the prospective NHS study and the NECC may have minimized any potential biases due to the case-control design. Since talc exposure was defined as at least once per week, such habitual exposure is less susceptible to recall bias than sporadic exposure.

23. In 2009, Wu et al. (48) conducted a population-based study of 609 cases of women and 688 controls between the ages of 18 and 74 residing in Los Angeles with histologically confirmed incident invasive or borderline ovarian cancers. Cases were identified through the Surveillance, Epidemiology and End Results (SEER) Program. Cases were matched to neighborhood controls on age and race/ethnicity. Controls were women with one intact ovary with no history of cancer except non-melanomatous skin cancer matched on age and race/ethnicity. Talc exposure was determined through a detailed interview by the same person which included a comprehensive questionnaire that used a reference date of 2 years before the date of diagnosis (or date of interview for controls). Talc use was reported as a yes or no metric (including yes or no for perineal area use), frequency and duration, total times of use, and total times of use before and after 1975. Few users of talc (24) had tubal ligation or hysterectomy prior to talc use and were considered as non-users.

The cases were primarily white woman but also included 41 African American women, 136 Hispanic women, and 51 Asian women. After adjusting for race, age, education, tubal ligation, family history, menopausal status, use of oral contraceptives, and parity perineal use of talc was associated with a statistically significantly increased risk of ovarian cancer (RR 1.53, 95% CI: 1.13-2.09). Elevated risks were also noted among those who used it on sanitary napkins, underwear and on diaphragms but not significant due to limited statistical power. There was a clear trend of increasing risk with increasing frequency of use among users who had used it for more than 20 years. The risk of ovarian cancer increased significantly with increasing frequency and duration of talc use; compared to never users, risk was highest among long duration (20 years), frequent (at least daily) talc users (RR 2.08, 95% CI: 1.34-3.23). The risk increased significantly with lifetime total times of talc use, but the association was limited to those who started talc use before 1975 (P_{trend} <0.001). The association between talc use and ovarian cancer was strongest for serous ovarian cancer. Risk of ovarian cancer increased with the diagnosis of endometriosis. Limitations include the rates of non-response among cases and controls, and classification of talc use among a small number of users with prior hysterectomy as being non-exposed. However, the effect of this misclassification is likely to be minimal.

24. In 2009, Moorman et al. (90) reported on a study involving 1,114 cases with histopathologically confirmed tumors as part of the North Carolina Ovarian Cancer Study. newly diagnosed cases were identified through the North Carolina Central Cancer Registry. All cases were confirmed by histopathologic review. Controls were frequency matched to cases and recruited from the same geographic region using random digit dialing. The controls could not have had a bilateral oophorectomy. Talc exposure was reported through in-person interviews conducted by nurses with life calendar and pictures of contraceptives, menopausal hormones, and other medications were used to help aid recall. Talc use was reported as a yes/no metric.

The analysis focused on invasive ovarian cancer which comprised of 78% of cancers for African-Americans and 79% for whites. Among controls, talc use was reported by 23.9% among whites and 31.2% of African-Americans. After adjusting for age there was an excess risk reported for both whites (OR 1.04, 95% CI: 0.82-1.33) and African Americans (RR 1.19, 95 % CI: 0.68-2.09) which were not statistically significant. Limitations include the high rates of non-response (33.5% among cases, 39.1% among controls), with higher non-response rates among African-Americans. There was a large proportion of missing data on talc use for cases and controls; 23.6% and 38.5% among whites, respectively, and 25.2% and 29.1% among African Americans, respectively, resulting in misclassification of exposure. The authors did not

clarify the route of talc exposure and may have classified non-genital talc exposure to the talc exposed group which may have diluted the RR. Additionally, the study did not adjust for confounders to address the timing, frequency and duration of talc exposure, or whether talc exposure occurred before or after tubal ligation or hysterectomy.

25. In 2011, Rosenblatt et al. (60) reported on a study of women between the ages of 35 and 74 from 13 counties in Washington state. Cases of borderline or invasive epithelial ovarian cancer were identified through the Cancer Surveillance System. Controls were selected from the population using digit dialing. Talc exposure was determined through in person interviews which included a reference period of unstated length before diagnosis or interview. For powder use on sanitary napkins and deodorant spray, the total number of months of use was recorded. For powder use on perineum after bathing, only intervals of at least one year when powder was usually used was recorded. Talc use was reported as genital powder exposure by type of use, duration of use, lifetime applications, age at first use, age at last use, calendar year of first use, time since first use, and time since last use.

Perineal use of powder after bathing was reported in 12% of controls. Reporting of cornstarch was uncommon in the study. After adjusting for age, calendar year of diagnosis, county of residence, number of full term live births, and duration of hormonal contraception the perineal use of powder after bathing was associated with an increased ovarian cancer risk (OR 1.27, 95% CI: 0.97-1.66) which was not statistically significant, but a statistically significant increased risk was seen among women with borderline tumors (OR 1.55, 95% CI: 1.02-2.37), similar to that reported by Harlow et al. (79) There were no differences in risk among various types of powder use, as the risk among those who reported use of talcum powder was RR 1.38 (95% CI: 0.77-2.47). There was no difference in exposure outcome relationship between talc use before and after 1980. There was no pattern of risk associated with perineal dusting powder and the increasing extant of use as defined by years in which it was used or number of lifetime applications. The participation rate of cases and controls was modest at 76.8% and 69%. Some misclassification of exposure is possible as participants may be unable to provide accurate information on whether the specific powder contained talc. However, the presence of talc, rather than a specific dose, is the primary determinant of exposure in which case genital powder use is a reasonable proxy for talc exposure.

26. Kurta et al. 2012 (91) reported on a case-control study from the Hormones and Ovarian Cancer Project using 902 ovarian cancer cases and 1802 controls. Participants were diagnosed with histologically confirmed ovarian, fallopian tube or peritoneal cancers. They were at least

9 years old and within 9 months of diagnosis. Controls were frequency matched by age and area code to cases at 2:1 ratio. Trained interviewers collected data via questionnaires. Perineal talc use was defined as ever using dusting powder or deodorizing spray on the genital or rectal areas, on sanitary napkins or underwear or on diaphragms or cervical caps.

Perineal talc use was reported among 20.9% of controls and 27.6% of cases. After adjusting for age, race, education perineal talc was associated with a statistically significantly increased risk of ovarian cancer OR 1.40 (95% CI: 1.16-1.69). Limitations include the population which was women seeking treatment for infertility which may limit generalizability.

27. In 2015, Wu et al. (53) evaluated 1,701 newly diagnosed histologically confirmed cases of invasive epithelial ovarian cancer cases of ovarian cancer among participants aged 18 and 74 in Los Angeles county identified through the USC Cancer Surveillance Program. Cases were primarily white but 308 Hispanic Women and 128 African American women were also included. Controls were selected from residents of LA county and were matched to cases on race/ethnicity and year of birth. Talc exposure was ascertained through in person interviews conducted using standardized questionnaires with a reference date of 12 months prior to diagnosis (or date of interview for controls). Genital talc was reported as no use or less than one year of use, yes use, and use per 5 years of talc.

Among controls the prevalence of talc use ≥ 1 year was 30.4% in non-Hispanic whites, 28.9% in Hispanics and 44.1%. After adjusting for several confounders including race, age group, menopausal status, age at menarche, hormone therapy use, BMI, income, education, life births, tubal ligation, oral contraception, endometriosis, and first-degree family history of ovarian cancer there was a statistically significant increased risk of ovarian cancer associated with genital talc use across all races (OR 1.46, 95% CI: 1.27-1.69), non-Hispanic whites (OR 1.41, 95% CI: 1.21-1.67), and Hispanics (OR 1.77, 95% CI: 1.20-2.62) compared to non-use or less than 1 year of use. The risk was elevated but not statistically significant among African-Americans (OR 1.56, 95% CI: 0.80-3.04) because of low statistical power for the subgroup. Every 5-year use of talc was associated with a statistically significant risk of cancer among the overall population (OR 1.14, 95% CI: 1.09-1.20) and non-Hispanic whites and Hispanics, whereas the excess risk among African-Americans was not statistically significant. The non-response rate for cases (36.8%) and controls was modest. There was no evidence of systematic bias in the ascertainment of exposure as prevalence of various conditions such as endometriosis was consistent with other prior studies.

28. Schildkraut et al. 2016 (52) evaluated African women aged 20-79 years of as part of the African-American Cancer Epidemiology Study. They selected 584 cases of newly diagnosed epithelial ovarian cancer and matched 745 controls to cases on age and region of residence using random digit dialing. Talc exposure was determined through a telephonic interview which included information on baby powder use. Participants were considered regular users if they reported use at least more than 1 time per month for 6 months. Regular users were asked about genital or nongenital use, frequency, duration, and lifetime applications (number of applications per month by number of months used). Since there was a small number of users who reported only genital powder use, they were grouped with genital and non-genital users to "any" genital use. Exposure was examined by frequency of use (less than 30 times per month, daily), duration of use (<20 years, ≥20 years) and lifetime number of applications (<3600, ≥3600). They also assessed for reporting biases and the effect of stimulant reporting because of the filing of class action lawsuits.

The median duration of body powder use in both cases and controls was 20 years and body powder use were reported among 52.9% of controls. After adjusting for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of oral contraceptive use, first degree family history of breast or ovarian cancer, and interview year there was a statistically significant increased risk of ovarian cancer with any genital powder use (OR 1.44, 95% CI: 1.11 to 1.86). There was a stronger association for ≥20 years of any genital powder exposure compared with <20 years of exposure and the test for trend was significant (P_{trend} =0.002). Similarly, the ORs for association between daily any genital powder users and EOC were larger in magnitude than never users, and the test for trend was significant (P_{trend} <0.01) There was also evidence of dose-response for any genital powder for the cumulative number of life-time applications with a higher risk among those with lifetime applications ≥3600; the test for trend was significant (P_{trend} <0.01). A stronger association was reported among post-menopausal women who used HRT compared to non-users. There was also an increase associated with non-genital powder exposure (OR 1.31, 95% CI: 0.95-1.79) which was not statistically significant. There was no evidence of statistically significant increased risk with "only" non-genital users and serous ovarian cancer but was statistically significant increased for non-serous ovarian cancer.

Limitations include the assessment of data by self-report. The underreporting of powder use in the abdomen which may reach the genital area may have resulted in a spuriously increased risk among "only" non-genital users or such an effect may be specific to African-American users. Although there was some evidence that there was more reporting of genital powder use

after class action lawsuits in 2014, recall bias alone is insufficient to explain these findings because there was a statistically significantly increased risk both before and after 2014.

29. In 2016, Cramer et al. (54) included 2,041 ovarian cancer cases from Eastern Massachusetts and New Hampshire as part of the Nurses' Health Study and the Ovarian Cancer Association Consortium. Pathology reports were reviewed to confirm diagnosis. The population was primarily white with less than 30 participants who were African Americans, Hispanics, Asians, or other race/ethnicities. Controls were identified through random digit dialing, driver license and town-resident lists and were frequency matched to cases by age and residence. Talc exposure was determined through in person interviews with a reference point 1 year prior to diagnosis or date of interview (for controls). Subjects were asked whether they regularly or monthly applied powder to the genital or rectal area, or on sanitary napkins, tampons or on other non-genital areas. Talc exposure was reported as personal use, potential exposure with no personal use (diaphragm, condoms, partner use), any genital powder use, type of genital powder use (cornstarch, baby powder, other), age of first use, time since exposure ended, frequency of use, years used, months per year of use, and total applications. Lifetime application was assessed by multiplying frequency of application per month with months of exposure. This was divided by 360 to yield talc years which were partitioned into separate quartiles for dose-response analysis. The study adjusted for a variety of confounders, with adjustments for age, study center, study phase, race, BMI, height, weight, parity, breastfeeding, oral contraceptive use, IUD use, ovulatory cycles, endometriosis or painful periods, Jewish ethnicity, family history, personal history of breast cancer, menopausal status, current smoking, ever smoked, asthma, alcohol consumption, and acetaminophen, aspirin or ibuprofen use.

Any genital powder use was reported in 26% of controls. The women who exclusively used cornstarch were considered unexposed. Most talc users began talc exposure around the age of 20. Overall, genital powder use was associated with a statistically significant increased risk of ovarian cancer (OR 1.33, 95% CI: 1.16-1.52) adjusted for age, study center and phase. BMI, smoking and alcohol use did not alter the association by more than 10% suggesting a lack of confounding. Most women reported using Johnson's Baby Powder and Shower to Shower with a trend for increasing risk by talc years. The trend for frequency of use was significant, but the trend for duration of use was flat. The talc ovarian cancer association was largely confined to premenopausal women and post-menopausal women with hormonal therapy. Sensitivity analysis indicated that the risk of misclassification of exposure in controls would have to very high (18%) to nullify the increased risk shown in the study. No data is available

on the extent of misclassification of talc exposure. Although some amount of misclassification is possible in retrospective studies, such a large amount is unlikely as shown by estimates from other analogous exposure-outcome association such as alcohol and breast cancer in the Nurses' Health Study. (114).

IX.III Cohort Studies. I will discuss the cohort studies below. However, it is important to emphasize that none of the cohort studies discussed below were designed to evaluate the association between talc use and ovarian cancer at the time of cohort assembly. In other words, evaluating the association between talc use and ovarian cancer was not the a-priori primary objective of the study but evaluated as a subsequent hypothesis, with its inherent limitations. For example, the NHS cohort was assembled in 1976 but data on talc use was not collected until 1982. (14). In contrast the primary objective of most case-control studies noted above was to evaluate the risk of ovarian cancer associated with talc use.

IX.III.I. In 2000, Gertig et al. (14) reported on an analysis from the U.S. Nurses' Health Study. 121,700 registered nurses were enrolled in the study; 78,630 were included in the cohort study; and 307 cases of ovarian cancer in 11 states. Notably, the Nurses' Health Study was a broad-based study of women's health. Ovarian cancer information was obtained through a questionnaire mailed to married female nurses 30-55 years which were updated every 2 years. Talc exposure was obtained from a survey question which asked "Have you ever commonly used talcum, baby powder, or deodorizing powder a) to apply to perineal (private) area? No, daily, one to six times per week, or less than once per week or b) to apply on sanitary napkins? No, Yes." Frequency was thus both reported as an "ever, never" metric as well as applications per week but duration of use was not recorded. Information gathered by a questionnaire requesting information on perineal talc use was ascertained only in 1982, and never updated during follow-up. Medical records were obtained for women reporting diagnoses of ovarian cancer or those participants who died (mortality follow up was 98% complete). Histologic subtypes of ovarian cancer were determined from pathology reports and classified as serous (cystadenocarcinoma and papillary adenocarcinoma), mucinous (mucinous papillary adenocarcinoma and adenocarcinoma), endometrioid (clear cell and mixed epithelial), and borderline. Cases of epithelial ovarian cancer (ICD 183.0) confirmed by medical record review or death certificate between 1982-1996 were included in the analyses. Participants who did not respond to the 1982 question on talc use were excluded, as were participants with cancer other than non-melanomatous skin cancer, bilateral oophorectomy, ovarian removal and those with radiation therapy. They included 307 cases of ovarian cancer among 984,212 person-years of follow up (0.03% PYs or 31.2/100,000 PYs). Information on covariates was obtained from the

biennial questionnaire and included oral contraceptive use, tubal ligation, parity, family history (not asked until 1992), smoking and BMI. Age adjusted incidence rates were calculated after adjusting for covariates above, as well as age at menarche, duration of breast feeding, age at menopause. 40.4% (n=31789) reported ever talc use of which 14.5% were ever daily talc users. Women who were talc users and did not have a tubal ligation had no increased risk of epithelial ovarian cancer with talc use- no evidence of interaction. There was an increased risk for histologic subtypes of ovarian cancer with talc use which was not statistically significant (RR 1.09, 95 % CI: 0.86-1.37) after adjusting for age, duration of oral contraceptive use, body mass index, tubal libation history, smoking status, and postmenopausal hormone use. While daily talc use on perineum (RR 1.12, 95% CI: 0.82-1.55) or use less than once/week (RR 1.14, 95% CI: 0.81-1.59) was associated with an excess risk which was not statistically significant, the point estimates for talc use on perineum 1-6 times/week (RR 0.99, 95% CI: 0.67-1.46) and on sanitary napkins (yes/no) (RR 0.89, 95% CI: 0.61-1.28) were lower than 1, and these confidence intervals may not rule out an increased risk. Importantly, there was a statistically significant increased risk for ever talc use for serous invasive cancers (RR 1.40; 95% CI: 1.02–1.91). For women who reported ever daily use, the RR for serous invasive cancer was 1.49 (95% CI: 0.98-2.26). The RRs for ever-users of less than 1 time/week and of 1-6 times/week were 1.29 (95% CI: 0.81-2.04) and 1.49 (95% CI: 0.77-2.11), respectively (P_{trend}=0.05). Women above age 45 in 1982 who reported ever talc use had a higher risk of serous invasive cancer (RR 1.51, 95% CI: 1.07-2.15).

The strengths of the study include the prospective design which reduces the risk of recall bias. The relatively short follow up period may have been unable to determine ovarian cancer. The NHS cohort was not primarily designed to evaluate the association between talc and ovarian cancer. Further, as discussed above, determining "never" use based only on a one-time question near the start of the study (14 years prior to terminating the study in 1996) introduces unidirectional "behavioral change" bias, likely misclassifying some "ever" users who used talc during the study as "never" users; and biased the findings towards the null. The exclusion of prevalent cases of ovarian cancer allows one to determine the influence of exposure on incident ovarian cancer, it also introduces an element of selection bias. Of the initial cohort of 121,700 volunteers, only 78,630 women were enrolled. It is not known whether any (or how many) of the 43,000 excluded women had ovarian cancer, nor whether any (or how many) of any such ovarian cancer volunteers excluded were talc users. They could not determine the intensity of exposure as they had no information on duration of talc exposure, or number of life-time applications or the age at which talc was initiated. The study was not a "new user design" and

used prevalent rather than incident users, and is susceptible to "prevalent user biases." (15) Prevalent users are "survivors" of the early period of talc use, which can introduce substantial bias if risk varies with time. This may bias findings towards the null due to the "depletion of susceptibles." They had no data on the intensity of exposure because there was no data on the duration of talc use, or number of life-time applications. The analysis on tubal litigation could not determine whether talc use was initiated after tubal ligation. Any such misclassification of exposure is also likely to be non-differential and bias towards the null.

As a continuation of the Nurses' Health Study, in 2010, Gates et al. reported on 924 cases of the ovarian cancer as part of Nurses' Health Study with ovarian cancer confirmed by a gynecologic pathologist review of medical records. (92). They evaluated the findings between risk factors for ovarian cancer and histologic subtypes of ovarian cancer and information on talc exposure was collected through biennial questionnaires. Talc use was reported as either greater than or less than once a week. After adjusting for body mass index activity, past smoking, current smoking, family history of breast or ovarian cancer, age, parity, parous status, breastfeeding, oral contraceptive use, tubal ligation, hysterectomy, age at natural menopause, and estrogen use they reported a non-significantly increased risk of all epithelial ovarian cancer (RR 1.06, 95% CI: 0.89 to 1.28) with genital talc use > once/week compared to < once a week. Although the estimates for the RR were higher for mucinous subtype (RR 1.50, 95% CI 0.84-2.66), there was no evidence of interaction across the subtypes ($P_{heterogeneity}$ =0.55) in this analysis. The strengths and weaknesses of this study are largely like the Gertig analysis of the NHS cohort above, with the additional limitations in the low number of cases (only 29 cases of epithelial ovarian cancer among genital talc users in 108, 870 women).

IX.III.II. In Houghton et al. (17) reported on finding from the Women's Health Initiative Observational Study (50-79 years at enrollment and post-menopausal). Among the 93,676 volunteers, only 61,576 participants were in the study cohort, and 429 adjudicated incident ovarian cancer (0.7%). Participants completed annual mailed questionnaires. Participants with bilateral oophorectomy, unknown number of ovaries, history of cancer (except non-melanomatous skin cancers were excluded). Perineal powder exposure (rather than specifically talc use) was obtained via self-report at baseline, and not updated during follow-up. Participants were asked whether powder had been used on genital areas, diaphragm or sanitary napkin or pad. If the participant answered affirmatively, there were further questions regarding duration of use where participants indicate use for less than 1 year, 1-4 years, 5-9 years, 10-19 years, or 20

or more years, but frequency of use was not recorded. The area of use was assessed dichotomously, and duration of use was categorized as never, 9 years or less and 10 years or more for analysis. Analysis was conducted for ever perineal powder use (ever use for any of the three categories) and duration for any powder use (maximum duration of any single area of application). Cancer cases were self-reported and confirmed through medical records including pathology reports. Data on covariates for age, race, education, alcohol, metabolic equivalents, smoking, recreational physical activity, oral contraceptive use duration, hormone replacement therapy, family history, age at last birth, BMI, self-reported family history of ovarian cancer were evaluated. They also evaluated reproductive factors such as age at menarche, age at menopause, age at first birth, age at last birth, parity, breastfeeding duration, history of tubal ligation, hysterectomy, irregular cycles, endometriosis. The covariates were obtained at baseline and not updated. The proportional hazards analysis was conducted to examine the risk of ovarian cancer and proportional hazards was tested using Schoenfied residuals. Participants with other cancers were still considered at risk for ovarian cancer. Covariates were selected for the multivariate analyses, if they had P-values of less than 0.1 during the backward regression until they had a parsimonious model. Additional variables from the literature were also included although they were not statistically significant. They analyzed ever perineal use, perineal use by application area, duration of use and combinations. Test for linear trend was evaluated across duration categories by modeling categories as continuous variables.

The average age of participants was 63.3 years at baseline with 12.4 years of mean follow-up. Most participants were white and were obese. Approximately 52.6% of the population reported ever use of perineal powder. Ever users were more likely to be heavier, used oral contraceptives and/or diaphragms. Perineal use of powder was associated with a 12% excess risk which was not statistically significant ($HR_{adj,}$1.12, 95% CI: 0.92- 1.36) whereas point estimates for use on sanitary napkins and diaphragms were lower than 1 but could not rule out an excess risk. Duration of perineal, sanitary napkin or diaphragms were not associated with ovarian cancer.
Strengths include the prospective design which reduces the risk of recall bias. Limitations includes the lack of information on whether the perineal powder use constituted talc use, and the inability to measure the frequency of exposure. It is possible that the analysis by duration included infrequent long duration users with short term frequent users which may result in bias towards null. Since exposure was not updated during follow-up, some never users who became ever users were misclassified as never users resulting in a bias towards the null. The exclusion of prevalent cases of ovarian cancer introduced an element of selection bias. Of the initial cohort

of 93,676 volunteers, only 61,576 women were enrolled; 10,622 volunteers who had already developed cancer at baseline were excluded. It is not known whether any (or how many) of these excluded women had ovarian cancer, nor whether any (or how many) were talc users. The inclusion of "prevalent users" rather than "incident users," leads to depletion of susceptibles and may bias findings towards the null. Data on covariates was not available after baseline resulting in the potential inclusion of participants (e.g., oophorectomy) not at risk of ovarian cancer and resulting bias towards the null. The generalizability of the study findings to younger pre-menopausal women is also unknown as the study findings are limited to older post-menopausal women (average age =63.3 years).

IX.III.III. In 2016 Gonzales et al. (93) examined the relationship between douching, talc use, and ovarian cancer among 50,884 women aged 35-74 years of age (84 % white and 64% post-menopausal) who had never had breast cancer but had a full or half-sister who with breast cancer. They excluded participants with bilateral oophorectomy and ovarian cancer. Among 41,654 participants 154 incident ovarian cancers (n=135 ovarian cancers) were reported (0.3%). Participants completed a telephone interview which included questions about reproductive history (oophorectomies), health and lifestyle and use of personal care products before enrollment, including the use of douching and use of genital talc applied as a powder or spray applied to underwear, sanitary napkin, diaphragm, cervical cap, or vaginal area. The frequency of use was categorized as no use, less than once a month, 1-3 times per month, 1-5 times per week, > 5 times per week, but duration of use was not recorded. As with the WHI and Nurses' study exposure was only measured at baseline and not updated during follow-up. Updated information on oophorectomy was collected during follow-up and information on cancer cases was collected via annual health update. Data on 37.6% of ovarian cancer cases was available only by self-report and the remainder confirmed by medical record review or death certificate. Cancer cases included tumors of the ovary, fallopian tubes, peritoneum, or of uncertain origin. Those who were BRCA1 or BRCA 1 positive test or those who had a sister with a positive test but had no report of negative test were considered BRCA positive. Cox proportional hazards analysis was conducted until diagnosis of ovarian cancer, oophorectomy, censoring or death. Generalized estimation equations was used to account for familial clustering at baseline. The proportional hazards assumption was evaluated by the goodness of fit test. A joint analysis of talc and douching use was also conducted. The included covariates were patency (yes or no for tubal ligation or hysterectomy), menopausal status, duration of OC use (none, < 2 2 to <10, 10 or more years), parity (yes/no) race and BMI.

The median duration of follow up was only 6.6 years. The average age was mean 57.8 years for cases. These cases were more likely to have a family history of ovarian cancer and carry a BRCA1 or BRCA2 mutation. More non-cases than cases used oral contraceptives. Talc use was only reported by 12% of cases and 14% of non-cases. Talc users were more likely to have BMI >30 kg/m^2. Talc use in the last 12 months after adjusting for race, BMI, parity, duration of oral contraceptive use, baseline menopausal status, and patency, was not associated with a statistically significant increased risk of ovarian cancer (HR 0.73, 95% CI: 0.44-1.20], but could not rule out an excess risk. There was no change in estimates when adjusted for douching. Douching at baseline, more common among talc users, was associated with increased risk of ovarian cancer (HR: 1.8 95% CI: 1.2-2.8).

There were significant limitations to the study. The authors acknowledge that an important limitation of their study was that they collected douching and talc information for the year before the study and did not account for the latency. As with the other two cohort studies, the Sister Study was limited by the issue of selection bias through the exclusion of women who had already developed ovarian cancer (and who could also have been lifetime talc users). Secondly, the Sister Study was vulnerable to behavioral change bias. The bias towards the null of this inaccurate assessment of "ever" user status prospectively, at the start of the study, was compounded by the fact that it was also vulnerable to retrospective inaccuracy, because it was based only on the 12 months preceding baseline. Thus, a participant who had last used talc 13 months before baseline would be categorized as a never-user, as would a participant who started using talc after baseline. Thirdly, the Sister Study's median follow-up of only 6.6 years is likely insufficient to detect any risk of ovarian cancer which likely takes more than 6.6 years to develop. The study also suffered from the limitations of prevalent user biases. Additionally, exposure was measured as ever/never use in 12 months prior rather than total applications resulting in non-differential misclassification towards the null. Data was only available by self-report on the diagnosis of ovarian cancer for many cases (37.6%) resulting in misclassification of outcome, which was likely non-differential and may bias findings towards the null. The study reported the lowest rate of talc use among the cohort studies (13.8%), further compounding the limited statistical power due to a short duration of follow-up. The generalizability of these findings is also limited as they included women without breast cancer who all had a family history of breast cancer and_may be at a higher risk (60%). The missing data were not missing at random and unclear whether analyses were adjusted for missing data. The authors concluded that the study

could not exclude a increased risk despite these findings. The study findings are limited to the predominant cohort of white post-menopausal women who constituted the majority of participants.

IX. IV. Summary of Findings from Epidemiological Studies.

1. The cumulative evidence from these studies demonstrates a statistically significant increased risk of ovarian cancer associated with perineal talc powder use which has been independently replicated by several investigators in different populations, different settings, across different sources using different study designs and time periods. Slight differences in magnitude of risk among these studies may reflect differences in inclusion or exclusion criteria and the accumulation of evidence over time and some variation due to chance. The updated meta-analyses in 2018, which have included all the studies, reported a statistically significant increased risk of perineal talc use and ovarian cancer, (41, 42), with little evidence of statistical heterogeneity or publication bias. The case-control studies provided 13,421 cases compared to 890 cases in the cohort studies. (42). Most case-control studies demonstrate an increased risk of ovarian cancer associated with talc use with an OR between 1.3 and 1.6, even after adjusting for various risk factors.

2. Meta-analysis which evaluate the association between perineal talc use and ovarian cancer have consistently shown an increased risk of ovarian cancer, (39, 41, 42, 73, 79), including pooled analysis using individual participant data. (10). My conclusions about the causal increase in the risk of ovarian cancer associated with talc exposure are heavily weighted by recent cumulative meta-analysis published in 2018, (41, 42). These meta-analyses provide the most comprehensive evidence base given the size of the study database and their methodologic superiority as assessed by the AMSTAR rating above. (Table 1). Also, importantly, there is no meta-analysis which has reported a statistically significant decreased risk of ovarian cancer with talc.

3. The only case-control study in which point estimates are below one was limited by the poor choice of controls and very high non-response rates. Despite these limitations it could not rule out a 21% increased risk of ovarian cancer associated with talc use which is not inconsistent with other studies. (86). Although the exposure rate to talc in the case-control studies has been variable in the control group from 5%-45%, this reflects the varying practices in the use of talc rather than the lack of an increased risk of ovarian cancer with talc use.

4. Although all studies are at potential risk of outcome misclassification, most of the studies used histologically verification for the diagnosis of ovarian cancer. Any such potential

misclassification of outcomes is likely to be non-differential and would have biased the findings towards the null.

5. There is no reason to believe, from the studies, that ovarian cancer would result in talc use, so the temporality of the association is established.

6. Case-control studies are susceptible to recall bias particularly when data on exposure are self-reported. However, several studies have included these questions on talc exposure as a part of larger questionnaires on other risk factors minimizing the possibility of recall bias. Recall bias is less likely to occur for chronic daily exposures such as talc as compared to intermittent short exposures. Further, recall bias is equally likely to affect other histologic types of ovarian (and endometrial) cancer but here the increased risk was limited to only epithelial ovarian cancer in most studies. Finally, the findings that only perineal talc use was associated with ovarian cancer but not with non-genital talc use argues against recall bias alone as a potential explanation of these findings.

7. Confounding is one potential explanation for these findings. However, several case-control studies adjusted for major confounders including the more recent case-control studies. (54). Although residual confounding is always possible in an observational study, studies that have reported adjusted and non-adjusted findings have reported similar results minimizing the impact of residual confounding. (41). Although there are some risk factors for ovarian cancer (e.g., genetic risk factors, family history, obesity and reproductive history), for any of them to be confounding to an extent that could account for the positive relations that have been reported, they would have to be strongly correlated with talc use. Family history, ethnicity, obesity and some reproductive risk factors are positively associated with the risk of ovarian cancer, but the magnitude of these associations does not appear high enough to introduce enough confounding, even jointly, to explain completely the positive association. To invalidate the statistically significant findings of an increased risk of ovarian cancer from the studies, one would have to postulate a degree of selection, recall bias and confounding pervasive across different time periods, different populations which is highly implausible.

8. Case-control studies are also at risk of selection bias which may introduce bias in both directions. As opposed to hospital-based controls, which may be less susceptible to selection bias, the population-based case-control studies have consistently showed a higher estimate of increased risk of ovarian cancer associated with talc use.

9. Reverse causality, where the diagnosis of ovarian cancer results in perineal use of talc, may be one possible explanation of the nonsignificantly increased risk in the group exposed to perineal talc. However, this is also likely minimal in the case of ovarian cancer in which most

cases present at advanced stages with abdominal bloating, and vaginal symptoms only occur in a small minority of cases.

10. One of the cohort studies reported an increased risk with perineal talc exposure and serous invasive cancer (14). The pooled results from all three cohort studies, reported an excess risk of ovarian cancer, (42) which failed to reach statistical significance because of several limitations. The duration of follow up was limited resulting in low number of events and inadequate statistical powder. The only cohort study which reported an inverse association between perineal talc use and ovarian cancer included several other cancers beyond the ovary (such as peritoneum, endometrial) (93), which may have diluted an increased risk. It had a very short duration of median follow up of approximately 6.6 years which is insufficient to ascertain the development of ovarian cancer. Since talc induced carcinogenesis occurs via a foreign body mechanism, the latency period required to demonstrate such an effect is long. Despite these limitations, the upper bounds of the confidence intervals exceeded one and could not rule out an increased risk of ovarian cancer with perineal talc use. The cohort studies were at risk of significant other biases. Exposure was measured at baseline and not updated during follow-up (14, 17), which may have misclassified those participants at baseline who were never users but used talc during the study as never users resulting in a bias towards the null. The exclusion of prevalent cases of ovarian cancer (some of whom may have been exposed to talc) may also bias their findings. (14, 17) The cohort studies were also susceptible to "depletion of susceptibles" biasing their findings towards the null. None of the cohort studies were primarily designed to study the association between genital talc use and ovarian cancer as their primary objective. Despite these limitations, the meta-analysis of cohort studies demonstrated a statistically significant increased risk of serous invasive ovarian cancer.

11. Ascertaining *dose response* relationship with talc and ovarian cancer is difficult because of the challenges in quantifying talcum powder use usually collected by self-reported data (frequency, amount and duration), timing and patterns of use (e.g. douching), and other individual factors (e.g. co-existence of inflammatory conditions such as endometriosis and or vaginal bleeding) resulting in differences in measurement of exposure across studies. The dose response depends on both the amount of talc exposure, the frequency of talc uses and the duration. It is difficult to quantify the amount of powder actually used and degree of perineal dusting that might constitute an ''application of talc.' Another factor that may affect the dose-response relationship is whether use occurred at a time when the female tract was open, the age of initiation of talc use since the talc/ovarian cancer association is modified by closure of the female tract as a result of tubal ligation or hysterectomy (79). The presence of other risk factors

such as post-menopausal status, cancers other than invasive serous ovarian cancer may make it difficult to ascertain a dose-response relationship among older post-menopausal. The lack of statistical trend (58, 60) in some earlier studies may reflect some of these challenges as well the lack of a monotonic dose response effect. The exposure-response data need to be interpreted in the context of mechanistic studies which report that talc accelerates the development of ovarian cancer in susceptible individuals through accelerating the redox state in epithelial ovarian cancer cells. (49). Thus, an assessment of the gradient through a monotonic dose-response curve may not provide a complete picture of the biological gradient. It unclear why nature would mandate an increasing mono-tonic dose-response mechanism for causation, and some have argued that among Bradford-Hill viewpoints it is difficult to know how dose-response should be modelled. (50). Cumulative lifetime exposure may be a more appropriate measurement of exposure given the inflammatory mechanisms by which talc induces the development of ovarian cancer. It is important to recall that if the carcinogenicity of talc induced ovarian cancer most likely resembles that of asbestos induced mesothelioma (with which it shares histologic similarities), asbestos induced mesothelioma does not have a dose-response relationship. In the case of asbestos induced mesothelioma, latency may be more important whereas in the case of talc induced ovarian cancer induced by inflammation latency may be of lesser importance.

12. Despite these challenges, several studies have shown evidence of dose-response as measured by an increased risk with increased frequency (51-55) or increased duration, (52, 54)or combination of frequency and duration of exposure. (48, 54). Some studies show a exposure-response trend, (54) and the most updated meta-analysis show evidence of duration dose and responsiveness. (42). In the individual participant data meta-analysis a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis, but no significant trend was seen when analyses were restricted to ever users. (10) Importantly, the most recent meta-analysis reported an evidence of dose-response with risk being higher among those with >3600 applications of talc compared to participants with <3600 applications. (42) Both of these categories of exposure were associated with an increased risk of ovarian cancer. None of the cohort studies were able to conduct meaningful dose-response analysis because they did not collect data either on duration, (14, 93) or frequency of exposure. (17).

X. BIOLOGICAL MECHANISMS OF TALCUM POWDER INDUCED OVARIAN CANCER.

Although not an absolute requirement for determination of causation there are multiple well-established biological and molecular mechanisms by which talcum powder products induce ovarian cancer. The key routes of exposure and biological mechanisms are noted below.

***X.I. Retrograde Migration of Talc Particles*.** Genital talc can migrate up to the fallopian tubes and ovaries and talc particles have been detected within the ovaries of women who report perineal talc use. Heller et al. detected talc in the ovaries of 24 women undergoing incidental oophorectomy demonstrating that it can reach the upper genital tract (64) although the fact that talc particle counts were unrelated to reported levels of perineal talc exposure reflects the challenges in measuring exposure to talc. Talc has been found deeply embedded within ovarian tumors, (65) and subsequent studies have confirmed that these are not due to contamination. (94). Talc has also been demonstrated in pelvic lymph nodes of women with perineal talc exposure.(66). Supportive evidence of migration comes from studies showing retrograde migration of additional particles such as starch after gynecological examination, (68) findings of a decreased risk of ovarian cancer with tubal ligation and hysterectomy in case-control studies, (87) and meta-analysis, (115) which may minimize exposure to inflammatory particles. Although an industry funded study performed by the Cosmetic, Toiletry, and Fragrance Association failed to detect translocation of "measurable quantities of talc' in monkey models, (67) the timing and techniques of assessment and intraspecies differences could not rule out migration of talc particles. The FDA response to Citizen's Petition 2014 concluded the *"potential for particles to migrate from the perineum vagina to the peritoneal cavity is indisputable'*. Johnson & Johnson and IMERYS documents also acknowledge migration. In one document it was stated, "A review of the literature suggests that it is biologically plausible for talc particles to migrate from the vagina to the peritoneal cavity and ovaries following perineal application." (63, 116).

***X.II. Inhalation of Perineal Talcum Powder*.** Inhalation of talcum powder is another potential route of exposure that is biologically plausible and can cause inhaled fibrous talc (and asbestos) fibers to reach the ovary and thus increase the risk of ovarian cancer in women using these products. Approximately 50 percent of talc particles in commercially available talcum powder are less than 10 microns in size, (117) which have the potential for inhalation and reach the alveolar regions of the respiratory tract. (118) Asbestos fibers can pass from the alveoli to the

lung interstitium, from which they can travel via the lymphatic system to the bloodstream and other organs including ovaries. (119, 120) Inhaled fibrous talc shares extensive physical and chemical similarities with asbestos, and inhaled fibrous talc generated from perineal application may also reach the ovaries by inhalation. This mechanism was confirmed in a September 2017 study, "Below the Waist Application of Johnson & Johnson Baby Powder," Longo, et al. showed that normal application of Johnson's Baby Powder can produce airborne asbestos and talc fibers which could be inhaled. (70).

X.III. Talcum Powder Induced Inflammation and Alteration of Redox Potential. Inflammation has long been understood to be an important mechanism underlying the development of ovarian cancer. (61). Inflammation may underlie ovulatory events because an inflammatory reaction is induced during the process of ovulation. Risk factors for ovarian cancer include endometriosis (i.e., ectopic implantation of uterine lining tissue) and pelvic inflammatory diseases (PID). (121). PID was associated with an increased risk of borderline ovarian tumors, particularly among women who had had multiple episodes of pelvic inflammatory disease in a meta-analysis. (122). Consistent with the inflammatory mechanism for ovarian cancer, a prospective nested case-control study from the Prostate, Lung, Colorectal and Ovarian Cancer has also shown that global markers of inflammation such as C-reactive protein, Interleukin L-1α, Interleukin-8 and Tumor Necrosis Factor-α are associated with a significantly increased in the risk of ovarian cancer. (123). Supportive evidence for the role of inflammation also comes from a meta-analysis showing a decreased risk of ovarian cancer with tubal ligation and hysterectomy. (115). Studies have demonstrated increased risk of ovarian cancer with talcum powder use, and increased risk of ovarian cancer with endometriosis. (87). This risk is 3-fold higher among women exposed to talc who have endometriosis. (48).

Oxidative stress in the form of reactive oxygen species (ROS) and reactive nitrogen species (RNS) plays a role in the pathogenesis, neo-angiogenesis (formation of new vessels) and the dissemination of both early and late stage epithelial ovarian cancer. (124, 125). Epithelial ovarian cancer cells manifest a persistent pro-oxidant state characterized by upregulation of certain key oxidant and downregulation of key antioxidant enzymes, (125) and the presence of oxidative stress triggers cancer cells to favor anaerobic metabolism. Oxidative stress induces phenotypic modification of tumor cells by altering cross-talk between tumor cells and surrounding stroma. Talc can alter this redox state and cause a marked increase in mRNA levels of the prooxidant enzymes, iNOS (nitrous oxide) and MPO (myeloperoxidase) in talc treated ovarian cancer cells as compared to control as early as 24 hours in all doses, (49) as well as a marked decrease in the

mRNA levels of the antioxidant enzymes catalase CAT, glutathione peroxidase (GPX), and superoxide dismutase (SOD3) providing a mechanism by which talcum powder products can induce the development of ovarian cancer.

Cancer antigen [CA-125] a tumor marker secreted by the epithelial cell for monitoring recurrence after treatment of ovarian cancer, was elevated when both normal ovarian cell lines [1.7 +/- 0.5-fold] and ovarian cancer cell lines [1.4±0.5 and 4.4±0.5-fold increase in OV90 and TOV-21G EOC cell lines] were exposed to talc, providing another molecular mechanism by which talc can increase the risk of ovarian cancer. (106).

Talc has been shown to increase proliferation, induce neoplastic transformation and increase ROS generation time-dependently in the normal human epithelial and granulosa ovarian cells and dose-dependently in the polymorphonuclear neutrophils. (71). In studies of human mesothelial cells, both nonfibrous talc and asbestos have shown evidence of genotoxicity. (109) Some have suggested that perineal talc use may also increase risk of ovarian cancer by the induction of anti-MUC1(monoclonal antibodies) possibly via heat-shock protein, (72) although the data are not definitive. (101).

X.IV. Carcinogenicity in Animal Studies. Among animal studies a study among rats demonstrated the development of papillary changes after intrabursal injection of talc. Such papillary changes may be precursors of serous papilloma precursors of epithelial cancers. (107). Another 2-year inhalation study with cosmetic grade talc in rats and mice showed evidence of carcinogenic activity in male (an increased incidence of pheochromocytomas of the adrenal gland) and female (increased incidences of alveolar/bronchiolar adenomas) rats and carcinomas of the lung and pheochromocytomas of the adrenal gland. (108). There was no evidence of carcinogenicity in mice. However, limitations of this study include the lack of a suitable control (e.g. titanium dioxide), alternative explanations of these findings via particle overload, (127) and the fact that ovulatory patterns in rats are not fully applicable to humans.

X.V. Presence of Asbestos and other carcinogens in Talcum powder products. In assessing the biological plausibility of talcum powder products as a cause of ovarian cancer, it is important to consider the constituents of talcum powder products including whether it contains known or suspected carcinogens. The presence of asbestos in talcum powder products can and does provide a plausible biological explanation of the development of ovarian cancer. (36, 37).

Occupational exposure to asbestos is a well-established causal agent for the development of pleural and peritoneal mesothelioma, larynx and ovarian cancer. (36, 127). Talc and asbestos also share chemical similarities. The carcinogenicity of asbestos relies on shape of particles with long thin fibers-such as those occurring in crocidolite asbestos being particularly carcinogenic. Although talc consists primarily of platy talc, it may also contain fibrous talc or other asbestiform minerals. Epithelial ovarian cancer, one most closely associated with talc, histologically most closely resembles mesothelioma providing further evidence of biological mechanisms. As Huncharek notes in their meta-analysis of ovarian cancer associated with talc dusted diaphragm meta-analysis on page 427 "*If one is exposed to a mixture of talc and asbestos, it is reasonable to expect a carcinogen effect as it contains a known carcinogen.*" (13). In addition talcum products contain fibrous talc, heavy metals and fragrance ingredients which are known or suspected carcinogens. (26, 33, 35, 36). Like the presence of Asbestos Fibers, the presence of these known or suspected carcinogens provide a plausible biologic explanation for the increased risk seen in the epidemiologic studies.

XI. ASSESSMENT OF CARCINOGENECITY OF TALC BY THE IARC IN 2006.

The International Agency for Research on Cancer (IARC) expert panel evaluates the carcinogenicity of various products using the following criterion after review of animal studies, experimental studies and epidemiological data. (128). The data is examined to determine whether there is *sufficient evidence, limited evidence, inadequate evidence, or evidence suggesting lack of carcinogenicity* for both cancer in humans and animals, respectively. The mechanistic and other relevant data are examined to *identify established and likely mechanisms and determines whether each mechanism could operate in humans*. The agents are then classified into several groups. Group 1 are agents *carcinogenic* to humans (e.g., asbestos,) (37), Group 2A are agents *probably* carcinogenic to humans, Group 2B *possibly* carcinogenic to humans, Group 3 agents which are *unclassifiable* and Group 4 agents which are *probably not carcinogenic* to humans.

In 2006 IARC concluded that perineal use of talc not containing asbestos or asbestiform fibers was possibly carcinogenic to humans (129) based on *limited evidence in humans for the carcinogenicity of perineal use of talc based body powder and the limited evidence in experimental animals for the carcinogenicity of talc* (93) (Group 2B-b). (38). Although a positive association has been observed between exposure to the agent and cancer for which causal interpretation is considered by the Working Group to be credible, but chance, bias, or confounding could not be ruled out

with reasonable confidence. For purposes of their evaluation, IARC considered 19 case-control studies and 1 cohort study. (14). The Working Group concluded that 8 of the more informative case-control studies (as well as most of the less informative ones) showed a consistent excess risk in the order of 30-60%. The cohort studies neither supported or refuted the evidence from case-control studies.

The IARC assessment was carried under the assumption that talcum powder products did not contain asbestos based on the published findings at the time- an assumption that is not supported by current data. In such a case, talcum powder products would be unequivocally classified as a Group 1 carcinogen like asbestos. Importantly, even absent a finding of asbestos in talcum powder products, the consistent cumulative evidence of peritoneal use of talcum powder products demonstrates an increased risk of ovarian cancer. Several *new systematic reviews based on recently published studies have further added to the accumulating evidence on an increased risk of ovarian cancer with talc use.* (10, 41, 42). *There is now further evidence of exposure response* relationships, with measured by an increased risk with increased duration (52, 54) or combination of frequency and duration (48) and the most updated meta-analysis show evidence of duration dose and responsiveness. (42). Finally, in addition to the epidemiologic evidence there is evidence from toxicology , molecular biology and other mechanistic data which supports my opinions .

XII. COSMETIC EXPERT REVIEW PANEL REPORT.

For the sake of completeness I also reviewed a report on the safety of cosmetic talc by an industry sponsored panel. (130). The panel was primarily composed of dermatologists, with limited expertise in epidemiology and carcinogenicity. The review was carried out under the flawed assumption that cosmetic-grade talc must contain no detectable fibrous, asbestos minerals and thus limited its assessment to animal and clinical studies on talc that did not contain asbestos, and erroneously concluded that there was no evidence of talc migration. As a result of these serious methodologic shortcomings and funding biases it arrived at its erroneous conclusions that talc was safe for use in cosmetics. (130) As discussed above, the findings of this panel have been superseded by findings from several new epidemiological studies, mechanistic studies and systematic reviews which have further added to the accumulating evidence on an increased risk of ovarian cancer with talcum powder product use.

XIII. ASSESSMENT OF CAUSALITY.

While talc is clearly associated with development of ovarian cancer, we must assess whether the observed association leads to an inference about causation. In 1965, in the President's Address to the newly-established Section of Occupational Medicine of the Royal Society of Medicine, Sir Austin Bradford Hill, Professor Emeritus of Medical Statistics at the University of London, attempted to encapsulate the aspects of a causal relationship, as it was understood at the time. (1). As he described them, they were: 1. strength of association, 2. consistency, 3. specificity, 4. temporality, 5. biological gradient, 6. plausibility, 7. coherence, 8. experiment, and 9. analogy. As Professor Hill explained, no aspect alone is either necessary or sufficient: "What I do not believe . . . is that we can usefully lay down some hard-and-fast rules of evidence that ***must*** be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence . . . and none can be required as the ***sine qua non***." Further, according to Professor Bradford Hill, these are not the only aspects of causation, but they are informative. It must also always be remembered, as highlighted in a recent statement by the American Statistical Association, that a lack of statistical significance does not imply lack of clinical significance (18) – a point also highlighted by Bradford Hill, who noted that while statistical tests can remind us of the role of chance, *"No formal tests of significance can answer those questions."*

With respect to the analysis at issue, that is, the association between talcum powder products and ovarian cancer—the results are not only statistically significant, but, as described above, have been replicated by several independent authors in multiple studies across a range of study designs. The cumulative body of evidence was appraised using the Bradford Hill viewpoints. In this regard, and as described in this report, I put significant weight on the Strength, Consistency, Temporality, Biologic Plausibility, and coherence factors and, to a lesser extent, Gradient (Dose-Response) and Analogy data to support my opinion that Talcum Powder Products can cause ovarian cancer. For the reasons stated below, I do not weigh heavily the Experiment and Specificity data in light of the totality of the evidence supporting a causal inference. My assessment is described below.

1. Strength of Association. This aspect of a causal relationship refers to the degree or magnitude of effect to which the exposure is associated with the outcome. (1). According to Bradford Hill , the more likely the exposure is associated with the outcomes, the more likely is it to be causal. As summarized in the meta-analysis in section above, I conclude that the association of talc with

ovarian cancer shows an approximate 30-60% relative increase in the risk of ovarian cancer, after adjustment for multiple confounders of the talc and ovarian cancer relationship. (10, 42). The strength of the association, replicated in multiple studies, provides evidence in support of a causal association**.** There are several noteworthy examples of well-established causal relationships (e.g. second hand smoking and lung cancer), (131) where the strength of the association is in the order of 20-40%. Such causal associations can have significant effects on the population if a large segment of the population is exposed, as in the case of air pollutants and myocardial infarction, which are significantly associated with an increase in MI risk with small relative risk (carbon monoxide: 1.048; 95% CI, 1.026-1.070; nitrogen dioxide: 1.011; 95% CI, 1.006-1.016; sulfur dioxide: 1.010; 95% CI, 1.003-1.017; PM_{10}: 1.006; 95% CI, 1.002-1.009; and $PM_{2.5}$: 1.025; 95% CI, 1.015-1.036) but a large population burden because of the large percentage of the population that is exposed. (47). Similarly, 75-100 mg of daily Aspirin has been shown to reduce the risk of cardiovascular events among those weighing 50-69 kg by 25 % [HR 0.75, 95% CI, 0.65-0.5] (132) in an individual participant data meta-analysis of randomized controlled trials. An increment of one serving a day of fruit and vegetables reduced all-cause mortality by 5% (HR 0.95 95% CI: 0.92 - 0.98) in a meta-analysis of cohort studies. (133). As discussed below, I place significant weight on the fact that studies demonstrate a strong association between talcum powder use and ovarian cancer and show consistency of the data.

2. Consistency. This viewpoint assesses whether the finding is repeated in different settings, place and time. (1). As shown in detail above, the direction and strength of association of talc and ovarian cancer is generally consistent across studies, including observational studies of various designs and their meta-analysis, and observational studies. These studies have been conducted in different clinical settings across the world, with different duration of follow up and the cumulative evidence has consistently shown a significantly increased risk of ovarian cancer with the use of talcum powder products. As expected, there are slight differences in the point estimates which reflect differences in study population with nearly all point estimates showing a direction of increased risk of ovarian cancer. The confidence intervals, however, across study designs overlap, indicating consistent results. I place significant weight on the fact that the consistency and strength of the association found in multiple independent studies demonstrates that the association is causative.

3. Specificity. This viewpoint considers whether the outcome of the disease appears to be specific to the exposure, (1) although since the original publication of the Bradford Hill we know

in most cases, absolute specificity for an exposure outcome association is not generally possible for many diseases, particularly cancer, and not required to provide proof of causation. Even the well-established, causal relationship between cigarette smoking and lung cancer or heart disease is not characterized by specificity. Genetic factors may also play a role in the occurrence of ovarian cancer. As discussed above, the occurrence of ovarian cancer is consistently higher among talcum powder users compared to non-users, even after adjusting for several confounders. I placed less weight on absolute specificity of the association between talcum powder exposure and ovarian cancer given the multi-causal nature of the outcome, particularly in light of the strength and consistency of association factors.

4. Temporality. The temporality viewpoint assesses whether the exposure always predates the development of disease. (1). In each of the epidemiologic studies noted above, talc exposure occurred before the diagnosis of ovarian cancer. Although some have argued that some of the symptoms of ovarian cancer (vaginal bleeding, irritation) may lead to talcum powder use, since most ovarian cancers present with abdominal bloating and advanced stages of the disease it is difficulty to attribute how development of ovarian cancer would lead to talc use (e.g., reverse causality). I placed significant weight that the exposure to talc preceded the development of ovarian cancer in the studies above.

5. Biological Gradient. This viewpoint assesses whether there is a biological gradient or dose-response effect, (1) recognizing that presence of dose-response is not an absolute requirement for causation. In order to determine dose-response, it is necessary first to determine dose. While the presence of a dose-response relationship supports a causal link, the absence of such a relationship does not preclude a causal association. The causal relationship between asbestos and mesothelioma, which most closely resembles the current scenario is not dose-dependent. Assessing dose-response is challenging in the context of perineal talc use for several reasons: first, unlike, say, birth-control pills, the amount of talc powder product use is not fixed, nor is the number of uses per time (day, week, or month). At a minimum, to assess total dose, it is necessary to acquire information about both duration and frequency. Ascertaining a dose-response relationship with talc and ovarian cancer is particularly challenging given that the risk of ovarian cancer may vary with age, premenopausal and post-menopausal status and the presence of other risk factors. The dose-response depends on both the amount of talc exposure, the frequency of talc uses and the duration. The presence of other risk factors such as post-menopausal status, cancers other than invasive serous ovarian cancer and the “depletion of

susceptibles" over time may make it difficult to ascertain a dose-response relationship. Several studies show evidence of dose-response as measured by an increased risk with increased frequency, (48, 51-55) or increased duration, (52, 54, 56) or a combination of frequency and duration of exposure. (52, 54). Some studies have also shown evidence of increased risk with increased number of lifetime applications, (10, 48, 52) which may be a more accurate measure for long term exposure outcome association mediated via inflammation. The most updated meta-analysis show evidence of duration dose and responsiveness, (42) with risk being higher among those with >3600 applications of talc compared to participants with < 3600 applications, although with overlapping confidence intervals. (42). Based on the above limitations with study design to ascertain dose effect, specificity of dosing of talc and the possibility of threshold effect, I find biological gradient less compelling, but still compelling of my causation analysis than the other Bradford Hill overviews as referenced above.

6. Plausibility. Although this is not a requirement for causation, an association that is biologically plausible is more likely to be causal. (1). While this viewpoint only requires biological mechanism to be *plausible*, which is necessarily limited to the state of biological knowledge at the time of assessment, evidence from the literature described in detail in the section in biological mechanisms shows multiple routes of exposure, multiple pathways and multiple mechanism by which talc can cause ovarian cancer. **Section X** demonstrates how talcum powder products can migrate to the ovaries, induce inflammation, alter redox potential resulting in a pro-oxidant state, (49) and act as a mutagen. (109). As a results of the significant body of evidence that has accumulated on biological mechanisms, I place significant weight on the fact biological plausibility provides evidence in support of the causal role of talc in the development of ovarian cancer and there is a highly biological plausible mechanism here for carcinogenicity which supports my opinion.

7. Coherence. This viewpoint assesses whether the cause-and-effect interpretation of data conflicts with the generally known facts of the natural history and biology of the disease. (1). The evidence on the risk of ovarian cancer with talcum powder exposure is consistent with the nature of the disease. Multiple studies suggest that talcum powder products have biological effects which plausibly explain the occurrence of ovarian cancer. Given the biological mechanisms related to inflammation described above, this mechanism and causal association itself fit easily within the current framework of scientific knowledge about the development of

ovarian cancer mediated by inflammation. I placed a significant weight on the coherence of findings in support of the causal role of talc in the development of ovarian cancer.

8. Experiment. Occasionally, in making a causation assessment, it is possible to appeal to experimental, or semi-experimental, evidence. The definitive experimental evidence would be a placebo controlled randomized trial among patients who are assigned to use talc and others who do not use talc in which the outcome of incident ovarian cancer would be actively ascertained. However, such evidence does not exist and would not be ethical nor feasible with a rare outcome such as ovarian cancer with an incidence of 11.4/100, 000 person-years noted above. While there is no randomized controlled trial here, that is common when dealing with a suspected cancer risk. For instance, there is no randomized controlled trial which supports the causal role of smoking in lung cancer. Such a trial to provide absolute proof of harm, which ignores the body of evidence that has accumulated and places patients at risk for developing ovarian cancer raises significant ethical concerns when data from robust observational studies and their meta-analysis have consistently shown an increased risk of ovarian cancer. In the absence of experimental evidence, this overview is weighted as less important than the other more important viewpoints noted above.

9. Analogy. Asbestos has been shown to cause ovarian cancer which offers an appropriate analogy, (40) but this viewpoint was considered less significant than other viewpoints noted above.

XIV. CONCLUSIONS.

Based on my background, training and education as a physician and epidemiologist, review and analysis of the totality of the evidence, using the weight of evidence analysis, including considering and weighting the Hill viewpoints, as described in this report, it is my opinion stated to a reasonable degree of scientific and medical certainty that peritoneal use of talcum powder products can cause ovarian cancer.

Signed this 16th day of November 2018

Sonal Singh

Sonal Singh, MD, MPH

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Table 1. AMSTAR (Assessing the Methodologic Quality of Systematic Reviews) Rating of Systematic Reviews and/or Meta-analysis of Genital Talc use and Ovarian Cancer

Criterion	**Harlow et al 1992[1]**	**Gross and Berg et al 1995[2]**	**Cramer et al 1999[3]**	**Huncharek et al 2003[4]**	**Langseth et al 2007[5]**	**Terry et al 2013 #[6]**	**Berge et al 2018[7]**	**Penninkilampi and Eslick 2018.[8]**	**Huncharek et al 2007 [9]***
A priori design	UA	Y	N	UA	UA	Y	Y	Y	UA
Duplicate study selection & extraction	N	N	N	Y	N	NA	Y	Y	Y
Comprehensive search	N	N	N	UA	N	NA	Y	Y	N
Status of publication used as criterion	UA	N	UA	Y	UA	NA	Y	N	Y
List of included & excluded studies	N	N	N	N	N	Y	Y	Y	N
Characteristics of studies provided	N	Y	N	N	N	Y	Y	Y	Y
Scientific quality of studies addressed	N	UA	N	N	Y	Y	Y	Y	N
Scientific quality of studies used in formulating conclusions	N	Y	UA	N	Y	Y	Y	Y	N
Methods of combining studies appropriate	N	Y	Y	Y	Y	Y	Y	Y	N
Likelihood of publication bias addressed	N	N	N	N	N	NA	Y	Y	N
Conflict of interest included	Y	Y	Y	UA@	Y	Y	Y	Y	UA@

*Meta-analysis by Huncharek et al in 2007 et al evaluated only talc on contraceptive diaphragms
Terry et al 2013 conducted an individual participant data pooled analysis so several items for systematic review NA
@ Incomplete financial disclosures of role of sponsor in meta-analysis
Y= Yes N= No; NA= Not applicable; UA : Unable to answer

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Additional Materials and Data Considered

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Other Materials

1. WCD000254-WCD000255
2. IMERYS210136-IMERYS210137
3. IMERYS241994-IMERYS242004
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8. JNJ000251888-JNJ000251890
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10. JNJ000460665-JNJ000460673
11. JNJ000526231-JNJ000526676
12. JNJAZ55_000000577-JNJAZ55_000000596
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17. JNJMX68_000004996-JNJMX68_000005044
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31. Educational report of Thomas Dydek
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EXHIBIT A

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Education

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Internal Medicine Residency, Unity Health System, affiliate University of Rochester
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Academic Appointments

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Assistant Professor, Dept of Medicine, Johns Hopkins Univ SOM — 7/2009 to 9/2016

Assistant Professor, Center for Public Health and Human Rights
Bloomberg School of Public Health, JHU (joint) — 7/2009 to 9/2016

Assistant Professor, Department of Medicine, Wake Forest University — 7/2007 to 6/2009

Instructor, Department of Medicine, Wake Forest University — 7/2005 to 06/2007

Employment History

Associate Professor, Department of Fam Medicine & Comm Hlth — 10/2016-present
Meyers Primary Care Institute & Department of Medicine (Joint)
University of Massachusetts Medical School
Role: Clinician- Investigator

Associate Professor, Department of Quantitative Health Sciences — 10/2018-present
University of Massachusetts Medical School
Role: Clinician- Investigator

Assistant Professor, Dept of Medicine, Johns Hopkins University. — 7/2009 to 9/2016
Role: Clinician- Investigator

Assistant Professor, Department of Medicine, Wake Forest University — 7/2007 to 6/2009
Role: Clinician- Educator

Instructor, Department of Medicine, Wake Forest University — 7/2005 to 6/2007

Role: Clinician- Educator

Residency (Medicine) Unity Healthy System, affiliate of the University of Rochester, Rochester, NY 7/2002 to 6/2005

Role: PGY 1, PGYII and PGY III Internal Medicine Resident

Research Associate, Clinical Pharmacology, Ohio State University 3/2001 to 6/2002
Role: Research assistant in clinical trials

Voluntary Research Associate, Clinical Pharmacology, Ohio State University 8/2000 to 2/2001
Role: Research assistant in clinical trials

USMLE STEP 1, II, III and Clinical Skills Exam Preparation 2/2000 to 7/2000
Role; Medical student

Resident, Medicine, Patna Medical College, Patna, Bihar, India 2/1998 to 1/2000
Role: Junior Resident in Medicine

Compulsory rotatory internship, Patna Medical College, Patna, India 12/97 to 12/98
Role: Fulfilling requirements for completion of medical degree in India

Certification and Licensure

Diplomate, American Board of Internal Medicine 8/2005-12/25

Massachusetts Board of Physicians 8/2016-8/2019

Physicians and Surgeons of Maryland (Inactive) 2009-2017

North Carolina Medical Board (Inactive) 2005 to 2009

Professional Memberships and Activities

Massachusetts Medical Society 2017-current

American College of Physicians 2003-2019

International Society of Pharmacoepidemiology 2011-current

Society of General Internal Medicine 2003 to 2016

International Society of Pharmacoeconomic Outcomes Research 2016 to 2017

Academy Health 2013

Global Health Council 2006 to 2010

Honors and Awards

Finalist W. Leigh Thompson Excellence in Research: Faculty Award, JHU	2016
Visiting Professor, Department of Medicine, Univ of Alabama	2013
3rd Best Abstract (trainee) 29th ICPE Montreal, Canada	2013
Bruce Squires Award for the Best Research Paper, CMAJ	2011
Scholars Abstract Award, Society for Clinical and Translational Sciences.	2010
Society of General Internal Medicine Clinical Investigator Award (Mid-Atlantic)	2010
Elected, Delta Omega Honorary Public Health Society, Johns Hopkins University	2008
Master Teacher Award, WFUSOM	2008
Tinsley R Harrison Faculty Outpatient Teaching Award, WFUSOM	2007
Tinsley R Harrison Faculty Outpatient Teaching Award, WFUSOM	2006
Senior–Resident Scholarship award, Unity Health System, NY	2005
ACP Health and Public Policy Scholarship, NY	2005

Committee Assignments and Administrative Services

American College of Physicians, Massachusetts Chapter, Health Policy Committee	2018
Chairs Advisory Council, Department of Fam Medicine & Comm Hlth	10/2016-present
American College of Chest Physicians, Cough Guideline Expert Panel	2017- present
Associate faculty, Welch Ctr for Prevention, Epi & Clin Research, JHU	2015 to 2016
Associate-Director, Center for Drug Safety and Effectiveness, JHU	2013 to 2016
Affiliate faculty, Center for Hlth Services and Outcomes Research, Johns Hopkins Bloomberg School of Public Health	2012 to 2016
World Health Organization, International Agency of Research on Cancer (IARC) Monograph- 108 Working group, Lyon, France.	2013

Preferred Items for Reporting of Systematic Reviews and Meta-analysis of harms Working Group Alberta Canada. 2012

Member, Health & Human Rights Working Group, JHU Center for Aids Research 2012

Core faculty, Center for Public Health and Human Rights, Johns Hopkins Bloomberg School of Public Health 2009 to 2016

Core faculty, Evidence-Based Practice Center, JHU 2009 to 2016

Medical Director, Outpatient Clinic, WFUSOM 7/2005-6/2009

Teaching Activities

Classroom

Comparative effectiveness research (2 cr), Johns Hopkins Medicine 2015 to 2016
Role: Developed course in CER for MD and MD/PhD trainees in the CTSA

Health and Human Rights, Johns Hopkins Bloomberg School of Public Health 2011 to 2015
Role: Annual lecture in the course for MPH students

Health Economic, Johns Hopkins Bloomberg School of Public Health 2013
Role: Annual lecture in the course for master's students

Pharmacoepidemiology, Johns Hopkins Bloomberg School of Public Health 2011-2015
Role: Annual lecture in the course for Masters and Doctoral students

Evidence-based Medicine, Johns Hopkins University School of Medicine 2012
Role: Course facilitator

Intro to Clinical Investigation, Johns Hopkins University School of Medicine 2012
Role: Annual lecture in the course

Clinical Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2010-2014
Role: Annual lecture in the course

Patient Physician and Society, Johns Hopkins University School of Medicine 2009
Role: Course facilitator

Clinical Teaching

Outpatient medicine 2016-2018

Role: Precepting residents and medical students in clinic at University of Massachusetts Medical School

Evidence Based Medicine 2012-2014
Role: Developed a novel course to teach Evidence based Medicine to Osler medical residents at Johns Hopkins University School of Medicine

Outpatient medicine 2005 to 2009
Role: Precepting residents in clinic at Wake Forest University

Inpatient Medicine 2005 to 2009
Role: Precepting internal medicine residents at Wake Forest University

Trainee /Junior Faculty Name	Mentoring Role	Title of Research Project/Paper	Current Position and Institution	Training Period
Univ of Massachusetts				
Mayuko Itofukunaga, MD	Faculty mentor	Systematic review of decision aids for lung cancer screening	Assistant Professor-Pulmonary Medicine and Critical Care	2017-18
Nathaniel, Erskine MD, PhD (student)	Scholarly activity	SR of herpes zoster and cardiovascular disease	MD/PhD Student Umass Med School	2017
Richeek Pradhan MS	Scholarly activity	Comparison of data on Adverse events	Phd Student McGill University	2017-18
Johns Hopkins Univ				
Omar Mansour	Scholarly activity	SGLT2inhibitors and cardiovascular outcomes	Masters student	2018
Geetha Iyer, MD	Faculty mentor	Multiple Pharmacoepidemiologic studies	Doctoral student, HSPH	2015-16
Sathiya Priya Marimathu	Faculty mentor	Generic drugs and patient oriented outcomes	MHS Student, JHMI	2015-16
Yohalakshmi Chelladurai, MD, MPH	RA Scholarly activity	Review of varenicline	Resident physician, Mercer, Atlanta	2013
Hsien-Yen Chang PhD	Faculty mentor	Pharmacoepidemiologic studies	Assistant Scientist at JHU	2011-15
Hasan Shihab, MD, MPH	RA Scholarly activity	Review of GLP-based therapies	Resident, Franklin Square, Baltimore	2013-14
Joshua Sclar, MD, MPH	Scholarly activity	Systematic review of attacks on health workers	General Preventive Medicine Resident	2013
Crystal Ng, MPH	Scholarly activity	Human Rights measures	MPH Student, JHSPH	2013
Ekta Agarwal, MPH	Capstone	Safety of novel anticoagulants	MPH student JHSPH	2013
Meijia Zhou, MHS	Scholarly activity	Adherence to novel anticoagulants	Doctoral student, Univ of Pennsylvania	2013
Kaitlin Hayman, MD	Capstone	SR of the impact of disasters On CVD outcomes	MPH student, JHSPH	2013
Wenze Tang, MPH	Scholarly activity	SCCS analysis of GIB bleeding with dabigatran	Doctoral student, HSPH	2013

Omar Mansour	Scholarly activity	SGLT2inhibitors and cardiovascular outcomes	Masters student JHSPH	2018
Shabana Walia MD	Scholarly activity	SR of CVD among refugees and displaced	ER physician, UT Houston	2016-2018
Wake Forest Univ				
Aman Amin, MD	Resident	Inhaled corticosteroids and pneumonia	Practicing internist, NC	2007-09
Apurva Trivedi, MD	Scholarly activity	SSRIs and bleeding	Gastroenterologist	2007-09
Other institutions				
Tonya Breaux-Shropshire PhD, MPH	Scholarly activity	Systematic review	Post-doctoral trainee, UAB	2015
Abhay Kumar, MD	Resident Scholarly activity	Wernicke encephalopathy after gastric bypass: systematic review	Assistant Professor St Louis University	2007

Current Grants and Contracts

Grants

(Ming Tai-Seale) 2/2016-12/2021
PCORI
Improving Patient-Centered Communication in Primary Care: A Cluster Randomized Controlled Trial of the Comparative Effectiveness of Three Interventions
The aim is to compare three interventions to improve patient communication in primary care
Role: co-investigator

(PI Jerry Gurwitz) 08/2018- 09/2019
NIH/NIA-1 R56 AG061813-01
Project Title: Controlling and Stopping Cascades leading to Adverse Drug Effects Study in Alzheimer's Disease (CASCADES-AD)
Role : co-investigator
The aim is to develop interventions to prevent prescribing cascades among those with Alzheimer's related Dementia (ADRD)

Past Grants

Death Data Exploration 08/01/17- 03/02/18
FDA Foundational Elements 3 HHSF223200910006I
Task Order Number: HHSF22301012T
Efforts to Develop the Sentinel Initiative HHSF223200910006I.
Role (Project Lead)

Effect of Therapeutic Class on Generic Drug Substitutions. 2014-2016
U01FD005267-01 (PI, Jodi Segal)

FDA 349,480
Role: Co-Investigator 0.6 CM

Comparative effectiveness Research & The Cochrane Eyes and Vision Group 2013-2016
U01 EY020522 (PI, Kay Dickersin)
NIH/NEI 825,397
Role: Co-Investigator 2.4 CM

Systematic review of gabapentin for neuropathic pain using multiple data sources 2015-2016
(PI, Caleb Alexander)
FDA Center of Excellence in Regulatory Science
Role: Co-Investigator (20% effort)

Integrating multiple data sources for meta-analysis to improve patient-centered outcomes research 2014-2016
(PI- Dickersin)
PCORI (ME-1303-5785) $698,174
Role: Advisor (2% effort)

Development of a scale for human rights violations. 2013-2014
(PI, Chaisson & Beyrer)
NIH Johns Hopkins Center for AIDS Research $ 18,873
Role: Pilot Awardee

Comparative effectiveness review of therapeutic options for obesity in the Medicare population.
Johns Hopkins Evidence Based Practice Center. 2013-2014
PI (Eric Bass)
AHRQ $125,000
Role: Project Principal Investigator (20% effort)

Center for Excellence in Comparative Effectiveness Education 2012-2013
PHRMA Foundation (PI Jodi Segal) Total Direct Cost: $250,000
Role: Co-investigator (5% effort)

A multi criteria decision analysis to assist with regulatory decisions around benefit and risk
Partnership in Applied Comparative Effectiveness Science: 2010 to 2013
PI (PI, Jodi Segal).
FDA $3,509,657
Role: Project Principal Investigator (25% effort)

Combination therapy vs. intensification of statin mono-therapy: An update. 2012-2013
PI (E. Bass- P.I of EPC.)
AHRQ
Role: Advisor (5% effort)

Troponin cardiac marker during renal impairment. 2012-2013
(E. Bass- P.I of EPC.)
Agency for Health Care Quality and Research
Role: Advisor (5% effort)

To develop an instrument for attacks on health workers. 2012-2013
PI (Len Rubenstein)
US Institute of Peace
Role: Co-investigator (10% effort)

To develop an instrument for attacks on health workers. 2012-2013
PI (Len Rubenstein)
McArthur Foundation $434,782
Role: Co-investigator (15% effort)

To conduct a benefit and harm assessment of *roflumilast* in COPD. 2012-2013
Johns Hopkins ICTR
Role: Co-investigator (5% effort)

To develop a China-JHU consultation for civil society public health professionals. 2012
Open Society Foundation $49,534
Role: PI (20% effort). Proposal for a public health training program.

PACER. 2012
PI (Rothman)
Google-Flu
Role: Coinvestigator (5%) Systematic reviewer and meta-analysis expert.

Methods for Balancing Benefits and Harms in Systematic Reviews
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2011-2012
AHRQ $188,871
Role: Project Task Leader and co-Investigator (10% effort)

Comparative effectiveness review of Meditation Programs for Stress and Wellbeing
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2011-2012
AHRQ $375,666
Role: Project Task Leader and co-Investigator (15% effort)

Comparative effectiveness review of prevention of VTE in special populations
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2011-2012
AHRQ $375,666
Role: Project Principal Investigator (20% effort)

To prevent and respond to gender-based violence (GBV) in refugee and conflict-affected populations. 2010-2011
(PI, Vu & Rubenstein) $293,946
Role: Co-investigator (10% effort)

Comparative effectiveness review of oral hypoglycemic medications
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2009-2010
AHRQ $125,000
Role: Co- Investigator (0% effort)

Johns Hopkins Clinical Research Junior Faculty Award. 2009-2012
NIH-KL2
ICTR
Role: Recipient (75% salary support)

Measuring exposure to human rights violations among men who have sex with men.
(PI, Mullany). 2009-2010
Center for Global Health Johns Hopkins $50,000
Role: Co-investigator (0% effort).

Research ethics for conducting research in vulnerable populations and unstable settings.
(PI, Mills) 2007-2009
CIHR $99, 887
Role: Co-investigator (10% effort).

Patents None.

Editorial work

Editor-in-chief and founder
BMC Conflict and Health 2007-12

Editorial Board Membership
Evidence Based Medicine (BMJ Group of Journals) 2017-current
Drug Safety 2008-16
American College of Physicians-PIER

Grant review 2012-current
Medical research foundation of New Zealand
Johns Hopkins Center for Public Health and Human Rights
Junior Faculty Research Grants
Medical Research Council of South Africa
Catalina Health Technology Assessment, Spain
Diabetes, UK
Johns Hopkins Medicine Research Council Synergy Awards
Johns Hopkins Institute for Clinical and Translational Research

Peer Review

1. *Acta Diabetologica*
2. *American Heart Journal*
3. *American Journal of Addictions*
4. *American Journal of Cardiovascular Drugs*
5. *American Journal of Managed Care*
6. *American Journal of Psychiatry*
7. *Annals of Internal Medicine*
8. *Annals of Medicine*
9. *Australian Medical Journal*
10. *BMJ*
11. *BMC Clinical Pharmacology*
12. *British Journal of Clinical Pharmacology*
13. *Bulletin of the World Health Organization*
14. *Chest*
15. *Circulation*
16. *Canadian Medical Association Journal*
17. *Clinical Pharmacology and Therapeutics*
18. *Clinical Trials*
19. *Cardiovascular Drugs & Therapy*
20. *Cochrane Collaboration*
21. *Disasters*
22. *Diabetolgia*
23. *Drug and Alcohol Dependence*
24. *Diabetes Obesity and Metabolism*
25. *Drug Safety*
26. *Epidemiology*
27. *European Journal of Neurology*
28. *European Journal of Pharmacology*
29. *European Respiratory Journal*
30. *Expert Opinion in Drug Safety*
31. *Global Public Health*
32. *Health Policy*
33. *International Journal of Epi*
34. *International Journal of Obesity*

35. Journal of the American College of Cardiology
36. Journal of the American Medical Association (5 in last 12 mo)
37. Journal of the American Medical Association-Internal Medicine
38. Journal of Cardiac Failure
39. Journal of Medical Case Reports
40. Journal of the Pancreas
41. Journal of General Internal Medicine
42. Medscape General Medicine
43. Medical Journal of Australia
44. Nephrology Dialysis Transplantation
45. North Carolina Medical Journal
46. Nutrition, Metabolism & Cardiovascular Diseases
47. Pediatric Infectious Disease Journal
48. Pharmacoepidemiology & Drug Safety-Best Reviewer Award 2013
49. Public Library of Science Medicine
50. Primary Care Respiratory Journal
51. Pediatrics
52. Research Synthesis Methods
53. Respiratory Medicine
54. Respirology
55. Southern Medical Journal
56. The Lancet
57. Thorax
58. Tropical Medicine & International Health

Abstracts and Presentations

Oral Presentations

National/International

1. GLP-1-based therapies and risk of pancreatitis: A matched case-control study. 29th International Society of Pharmacoepidemiology, Annual Meeting, Montreal Convention Center, August 26. Montreal, Quebec, Canada.2013
2. GLP-1 based therapies and risk of pancreatitis. 36th SGIM Annual Meeting, Denver, Colorado Posters. 2013
3. Risk of fractures with inhaled corticosteroids in COPD: Systematic review and meta-analysis of randomized controlled trials and observational studies, Society of General Internal Medicine, Minneapolis, Minnesota. 2011

4. Odds of fractures with inhaled corticosteroids in COPD: Systematic review and meta-analysis of clinical trials and observational studies, 27th International Society of Pharmacy-Epidemiology, Annual Meeting, Hyatt Regency August 24th. Chicago, Illinois. 2011

Local/Regional

Not applicable

Posters

National/International Meetings

1. Diagnostic algorithms for cardiovascular death in administrative claims databases. A systematic review 2018. International Society of Pharmacoepidemiology, Prague, August 24, 2018.
2. Risk of gastrointestinal bleeding among dabigatran users-a self-controlled case series analysis. Health Care Systems Research Network, San Deigo, March 22, 2017.
3. GLP-1 based therapies and risk of pancreatitis. Pancreatitis, Diabetes, and Pancreatic Cancer Workshop. NIH, Bethesda, Maryland. 2013
4. Thiazolidinediones and risk of bladder cancer: A systematic review and meta-analysis. 36th SGIM Annual Meeting, Denver, Colorado.2013
5. Who is the patient's doctor? Primary care responsibility and co-management relationships among generalist and non-generalist physicians in the National Ambulatory Care Survey, 2002 SGIM 29th Annual Meeting, Los Angeles, California.2006
6. The educational value of case reports from the SGIM national meeting in the internal medicine clerkship. SGIM 29th Annual Meeting, Los Angeles, California.2006
7. Using IPod technology to create a self-guided clinic tour for resident orientation SGIM 29th Annual Meeting, Los Angeles, California.2006
8. Narcotic management in chronic non-malignant pain. A survey of resident's knowledge and attitudes. SGIM 29th Annual Meeting, Los Angeles, California.2006
9. Formulary conversion programs pose a significant risk to patients, SGIM 27th Annual Meeting, Chicago, Illinois.2004

Local regional meetings

Inhaled corticosteroids and the risk of fractures in COPD: A systematic review and meta-analysis. DOM Annual retreat, Johns Hopkins University 2011

Invited presentations

National/International

1. Oral direct acting antivirals and the incidence or recurrence of hepatocellular carcinoma. NIH Collaboratory Grand Rounds [Web] March 2, 2018
2. Resurgence of hepatocellular carcinoma in the era of oral direct acting antivirals. Cause or Consequence? Fundamentals of Biomedicine Seminar Series. Texas Tech University Health Sciences Center. El Paso, Texas Dec 13, 2017

3. Aligning evidence with preferences: Methodological Challenges and Opportunities. - Department of Medicine. Dartmouth-Hitchcock Medical Center, Dartmouth, New Hampshire, June 15, 2016
   - Dartmouth-Hitchcock Medical Center, Dartmouth, New Hampshire, June 15, 2016
   - Department of Health Services and Research, Michael De-Bakey VA and Baylor University, Houston, Texas, May 16, 2016.
   - Meyers Primary Care Institute and Department of Family and Community Medicine, University of Massachusetts, Massachusetts, March 31 and June 9 2016.
   - VA Center for Chronic Disease and Outcomes Research, Minnesota VA, March 2016.
   - Department of Medicine. University of Central Florida, Orlando, Florida, November 2015.
   - Center for Health Policy and Research Grand Rounds. UC Davis, Sacramento California, Oct 9 2015;
   - Center for Evidence and Outcomes, Agency for Health Care Research and Quality. Gaithersville Maryland, August 31, 2015.
4. Risks of Spiriva Respimat outweigh its benefit: A Debate. Inhalation Asia, University of Hong Kong, Department of Pharmacology and Pharmacy, Hong Kong. 2013
5. GLP-1-based therapies and risk of pancreatitis. Center for Clinical Epidemiology and Biostatistics Seminar Series, Philadelphia, Pennsylvania. 2013
6. Visiting Professor. Department of Medicine. University of Alabama. 2013
7. Value based health care: Can shared decision making methods get us there? Center for Value and Effectiveness, Medicine Institute, Cleveland Clinic, Noon Conference.2013
8. Role of Multi-criteria decision analysis in regulatory policy
   - Stanford Prevention Research Center, Stanford University, Palo Alto, Stanford, California. 2013
   - South Carolina College of Pharmacy, Columbia, South Carolina.2013
   - Department of Medicine. UC Davis, Sacramento, California.2013
   - Department of Clinical Sciences, UT Southwestern, Dallas, Texas.2013
   - Department of Medicine, Geisenger Medical Center, Danville, Pennsylvania. 2013
9. Weighing benefits and risks: Role of shared decision making in type 2 diabetes. CTSA Grand Rounds, Mayo Clinic, Rochester, Minnesota. 2013
10. Are long-acting muscarinic agents safe for patients with COPD: A Debate. Airway Vista, Asan Medical Center, Seoul, Korea
11. Academia and industry collaboration for cardiovascular risk mitigation. CBI and Applied Clinical Trials. 6th Annual Summit, Closing Address. Ritz Carlton, Arlington, Virginia.2012
12. Varenicline: Where are we today? Tobacco Disease Research Program, UCSF. San Francisco California. Varenicline debate.2012
13. The Maoist Insurgency in Nepal: Health Systems Challenges and Opportunities Conference on Health in Fragile States: Challenges for the Next Decade. United States Institute of Peace. Washington DC.2011

14. Standards of Care and the Role of Community Advocacy in Clinical Trials. Clinical Research in Developing Countries, IIIrd Annual Marcus Evans Conference, Washington, DC.2008
15. Nepal-A Case study. Integrating public health methods into Conflict Analysis. Norman Patterson School of International Affairs, Carleton University, Ottawa, Canada.2007

Local/Regional

1. Oral direct acting antivirals and the incidence or recurrence of hepatocellular carcinoma. Research Seminar Series, Department of Family Medicine and Community Health. University of Massachusetts Medical School. June 15.2018
2. Safety of novel anticoagulants vs warfarin- a case study using complementary study designs. Quantitative Health Sciences, University of Massachusetts Medical School, February 28, 2017
3. GLP-1-based therapies and risk of pancreatic adverse events. University of Maryland, Division of Endocrinology, Metabolism and Nutrition, Grand Rounds, Baltimore, Maryland. 2013
4. Thiazolidinediones and Patient-Oriented Outcomes in Type 2 Diabetes, GIM Grand Rounds. Johns Hopkins University School of Medicine. 2012
5. Patient-Centered Benefit and Risk Assessment. Center for Health Services and Outcomes Research. Johns Hopkins University 2012
6. Varenicline and cardiovascular and neuropsychiatric adverse events: Do benefits outweigh risks? Welch Center Grand Rounds. Johns Hopkins University. 2011
7. The new wave, HIV, Human Rights and Men who have Sex with Men in Nepal. Johns Hopkins Bloomberg School of Public Health, 2011.
8. Network Meta-analysis and Serious Adverse Events. Network Meta-Analysis Methods Workshop. Johns Hopkins Bloomberg School of Public Health. 2010
9. Thiazolidinediones and Cardiovascular Outcomes in Type 2 Diabetes. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2008
10. How Safe Are Our Drugs and How Do We Know? North Carolina ACP, Durham.2008
11. Clinico Pathologic Conference. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2007
12. Globalization and Health Equity: An emerging Challenge for Academic Medicine. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2007
13. Thiazolidinediones and Cardiovascular Disease: The Seduction of Common Sense. Epidemiology Seminar Series, Public Health Sciences. Wake Forest University 2007

Workshops and Precourses

1. ISPOR National Meeting, Next Generation Comparative Effectiveness Research- Are we getting organized to facilitate research for the individual patient? Washington, DC May 24, 2016 (workshop)
2. SGIM national meeting, developing high-quality search strategies for systematic reviews. 2010
3. SGIM national meeting, Systematic Review. 2009

Peer reviewed original research publications (reverse chronological order)

*Trainees **

1. **Singh S**, Fouyazi H, Anzuoni K, Goldman L, Min JY, Griffin M, Grijalva CG, Morrow JA, Whitmore C, Leonard CE, Selvan M, Nair V, Zhou Y, Toh S, Petrone A, Williams J, Fazio-

Eynullayeva E, Swain R, Cole DT, Andrade S. Diagnostic algorithms for cardiovascular death in administrative claims databases. A systematic review. Drug Safety 2018 (accepted)

2. **Singh S,** Zeiman S, Alan Go, Fortmann S, Wenger N, Fleg JL, Radziszewska B, Stone NJ, Zoungas S, Gurwitz J. Statins for Primary Prevention in Older Adults – Moving toward Evidence-Based Decision-Making. *J Am Geriatr Soc. 2018 Oct 2. doi: 10.1111/jgs.15449. [Epub ahead of print]*
3. Tisminetzky M, Nguyen HL, Gurwitz J, McManus D, Gore J, **Singh S**, Yarzebski J, Goldberg RJ. Magnitude and impact of multiple chronic conditions with advancing age in older adults hospitalized with acute myocardial infarction. *International Journal of Cardiology. Published* Online: August 22, 2018. https://doi.org/10.1016/j.ijcard.2018.08.062.
4. Chang HY, **Singh S**, Mansour O, Baksh S, Alexander GC. Association Between Sodium-Glucose Cotransporter-2 (SLGT-2) Inhibitors and Lower Extremity Amputation: A Retrospective Cohort Study. JAMA Internal Medicine 2018. 10.1001/jamainternmed.2018.3034 http://dx.doi.org/10.1001/jamainternmed.2018.3034. August 13, 2018
5. Birring SS, Kavanagh JE, Irwin RS, Keogh K, Lim KG, Ryu JH; **CHEST Expert Cough Panel**. Treatment of Interstitial Lung Disease Associated Cough: CHEST Guideline and Expert Panel Report. Chest. 2018 Jul 20. pii: S0012-3692(18)31075-4. doi: 10.1016/j.chest.2018.06.038. [Epub ahead of print]
6. **Singh S**, Nautiyal A, Loke YK. Oral Direct-acting antivirals and the incidence or recurrence of hepatocellular carcinoma: a systematic review and meta-analysis. Frontline Gastroenterology Published Online First: 30 July 2018. doi: 10.1136/flgastro-2018-101017
7. Chang AB, Oppenheimer JJ, Rubin BK, Weinberger M, Irwin RS; **CHEST Expert Cough Panel**. Chronic Cough Related to Acute Viral Bronchiolitis in Children. Chest. 2018 Apr 26. pii: S0012-3692(18)30632-9. doi: 10.1016/j.chest.2018.04.019. [Epub ahead of print]
8. Haar RJ, Risko CB, **Singh S,** Rayes D, Albaik A, Alnajar M, et al. (2018) Determining the scope of attacks on health in four governorates of Syria in 2016: Results of a field surveillance program. PLoS Med 15(4): e1002559. https://doi. org/10.1371/journal.pmed.1002559
9. Pradhan R, * **Singh S.** Comparison of data on Serious Adverse Events and Mortality in ClinicalTrials.gov corresponding journal articles and medical reviews: A cross-sectional analysis. Drug Safety 2018 Apr 11. doi: 10.1007/s40264-018-0666-y. [Epub ahead of print]
10. Wu CH, Tu ST, Chang YF, Chan DC, Chien JT, Lin CH, **Singh S**, Dasari M, Chen JF, Tsai KS. Fracture liaison services improve outcomes of patients with osteoporosis-related fractures: A systematic literature review and meta-analysis. Bone. 2018 2018 Jun; 111:92-100. doi: 10.1016/j.bone.2018.03.018. Epub 2018 Mar 16
11. Field SK, Escalante P, Fisher DA, Ireland B, Irwin RS; **CHEST Expert Cough Panel**. Cough Due to TB and Other Chronic Infections: CHEST Guideline and Expert Panel Report. Chest. 2018 Feb;153(2):467-497. doi: 10.1016/j.chest.2017.11.018. Epub 2017 Nov 28.
12. Erkskine NA, *Tran H, Levin LL, Ulbricht CM, Fingeroth JD, Kiefe CI, Goldberg RJ, **Singh S.** A systematic review and meta-analysis on herpes zoster and the risk of cardiac and cerebrovascular events. PLoS One 2017 Jul 27;12(7): e0181565
13. **Singh S**. Nautiyal A. Aortic dissection and aortic aneurysms associated with fluoroquinolones: a systematic review and meta-analysis of observational studies. American Journal of Medicine 2017;130(12):1449-1457

14. Marimuthu S, Iyer G, * Segal JB, **Singh S**. Patient-relevant outcomes associated with generic tamsulosin, levothyroxine, and amphetamine in the FAERS: A pilot study. J Comp Eff Res. 2017;6(5):437-447.

15. Iyer G, *Marimuthu S, *Segal JB, **Singh S**. An algorithm to identify generic drugs in the FDA Adverse Event Reporting System. Drug Safety 2017 2;40(9):799-808.

16. Tang W, *Chang HY, *Zhou M, * **Singh S**. Risk of gastrointestinal bleeding among dabigatran users-a self-controlled case series analysis. *Sci Rep* 2017 Jan 20; 7:40120. doi: 10.1038/srep40120.

17. Onasanya O, Iyer G, * Lucas E, Lin D, **Singh S**, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. *Lancet Diabetes Endocrinol*. 2016 ;4(11):943-956

18. **Singh S**, Wright EE, Kwan AY, Thompson JC, Syed IA, Korol EE, Waser NA, Yu MB, Juneja R. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2017;19(2):228-238

19. Alexander GC, Iyer G, Lucas E, Lin D, **Singh S**. Cardiovascular risks of exogenous testosterone among men. *Am J Med*. 2017 ;130(3):293-305

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None

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Development of major curricular offerings.

2 credit Course for MD and MPH in comparative effectiveness research for the Johns Hopkins ICTR 2015-2016

Sonal Singh MD, MPH received his MD from Patna Medical College India (1999). He completed internal medicine residency training at Unity Health System, affiliate of Strong Memorial Hospital Rochester, NY. (American Board of Internal Medicine 2005) He obtained an MPH from Johns Hopkins Bloomberg School of Public Health (2008) and completed subsequent research training at the Johns Hopkins Hospital (2012) as a Junior Faculty Research Scholar supported by the National Institute of Health. He was the Associate Director for the Center for Drug Safety and core faculty Evidence Based Practice Center and the Center for Public Health and Human Rights at Johns Hopkins University. He has taught and held faculty appointments at Wake Forest University School of Medicine and Johns Hopkins University. He has received numerous awards including the Senior Scholarship Award from the Unity Health System (2005), Tinsley R Harrison Teaching Award for Education at Wake Forest University in 2007, Master Teacher Award at Wake Forest University (2008), Mid-Atlantic Society of General Internal Medicine Clinician Investigator of the Year Award (2010), the Bruce P Squires Award for the best research paper of the year from the Canadian Medical Association Journal (2011) and the third best student abstract award from the International Society of Pharmacoepidemiology (2013). He conducts clinical research with a focus on evidence synthesis, drug safety and shared decision making. Dr Singh has conducted research in several countries and has published more than 150 academic manuscripts to advance research and clinical care. His research efforts have been supported by the NIH, FDA, Agency for Health Care Research and Quality and the Patient Centered Outcome Institute and various private foundations. His research has been published in *Science, NEJM, Journal of the American Medical Association, Annals of Internal Medicine, Lancet and the British Medical Journal*, and featured in various outlets including Nature Medicine, NYTIMES, CNN, Washington Post and the Wall Street Journal. He currently serves on the editorial board of the *Evidence Based Medicine Journal* published by the BMJ, as a panel member of the American College of Chest Physician guideline writing group, and American College of Physicians Health Policy committee (Massachusetts chapter) He has served as a consultant to the World Bank, World Health Organization International Agency for Research Cancer, the Agency for Health Care Research and Quality, pharmaceutical sponsors and research firms and several non-governmental organizations. He is a practicing general internist with a passion for managing patients with complex medical conditions.

EXHIBIT B

Trial Testimony

I have not provided trial testimony.

Expert deposition (last 5 years)

1. US District Court of South Carolina, Charleston; *In Re Lipitor (Atorvastatin Calcium) marketing, sales practices and products liability litigation*, MDL No. 2:14-mn-02502-rmg, April 28, 2015; supplementary deposition, in 2016.
2. US States District Court, Eastern District Court of California; *Kristi Lauris Individually and as Successor in Interest to the Estate of Dainis Lauris; vs Defendants Novartis AG*, Case No. 1:16 cv 00393 –LJO-SAB. Case 2:17-cv-14302-RLR Document 49 Entered on FLSD Docket, 2017.
3. Circuit Court of Camden County, Missouri; *Grace Arlene Rahmoeller v. Walmart Stores, Inc. and Nicholas B. Collins*, Case No.: 15CM-CC00238, April 16, 2018.
4. US District Court, Southern District of Florida, *Dennis McWilliams and Lori McWilliams v. Novartis AG and Novartis Pharmaceuticals Corp.*, Case No. 17-14302, May 2, 2018.
5. *Mary Brufett and Jefferey Brufett, vs Iskra Pusic, MD, Keith E. Stocker Goldstein and Washington University*, Cause No 1622-CC01117 (Division 8), May 10, 2018.
6. US District Court Northern District of California, San Francisco Division; *In Re: Viagra (Sildenafil Citrate) and Cialis (Tadalafil) Products Liability Litigation*, Civil Case No.: 3:16-md-02691-RS, MDL No. 2691, August 9, 2018.

Exhibit 24

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

RULE 26 EXPERT REPORT OF
JUDITH ZELIKOFF, PHD

Date: November 16, 2018

Judith Zelikoff, PhD

I. BACKGROUND AND QUALIFICATIONS

I received my Ph.D in Experimental Pathology and Immunology at Rutgers: NJ Medical School (formerly known as University of Medicine and Dentistry of NJ) in 1982, after receiving a Master's degree from Fairleigh Dickinson University in Microbiology. My post-doctoral training was in toxicology at the NYU School of Medicine, Department of Environmental Medicine as a National Heart Lung Blood Institute (NHLBI) fellow.

I am currently a tenured-professor in Toxicology at NYU. As part of the NYU NIEHS (National Institute of Environmental Health Science) Center of Excellence, I serve as Director of the Community Engagement Core. In this capacity, I engage with environmentally-impacted underserved communities throughout New Jersey and New York to better engage the community to achieve long-term and sustainable outcomes, processes, relationships, discourse, decision-making, and implementation regarding environmental health. These goals are carried out through town hall meetings, focus groups, listening sessions, forums on relevant environmental concerns, surveys, as well as outdoor and indoor measurements of toxic metals such as lead, cadmium, mercury, and arsenic in water, air, and soil. I also provide service to the NYU School of Medicine as a member of the Grievance Committee, Institutional Animal and Use Committee (IACUC) and as an NYU Senator representing the School of Medcine.

I have served in numerous leadership positions in the field of toxicology, including NIH Study Sections, United Nations Environmental Programme, NASA boards, and National Academy of Science Panels (i.e., Institute of Medicine, National Research Council and Engineering, and Medicine's Board on Earth Sciences and Resources), as well as Environmental Protection Agency study sections and advisory boards concerning the toxic effects of air pollution, metals, and alternative tobacco products. Furthermore, I served for two years (2010-2012) as a member of the National Toxicology Program (NTP) Board of Scientific Advisors. In this capacity, I reviewed documents and provided input and guidance on the toxicity of various chemicals that were nominated for review and sent to the NTP for study and/or discussion. In some cases, we also decided on the carcinogenicity of specific compounds. I was not part of the NTP 10 ROC or 12 ROC, both of which deferred the decision on talc.

In addition, I presented about 150 international/national papers in the areas of toxicology and environmental and public health. I have organized several international toxicology meetings, served as editor for several toxicology/environmental public health books and authored numerous book chapters in the same areas. I have over 125 publications and book chapters in the area of immunotoxicology (for which I received a Lifetime Achievement Award from the Society of Toxicology), air pollution toxicology, metal toxicology, immunotoxicology, and developmental and reproductive toxicology associated with inhaled metals, mixtures, nanomaterials, dusts (i.e., World Trade Center Dust), and tobacco/nicotine toxicology.

I have held numerous executive positions in the Society of Toxicology (SOT) which includes three years as Secretary on the SOT Executive Council and one year as Chair of the Education Committee and Committee for Diversity Initiatives Committees. I have also provided leadership for four individual SOT Specialty Sections (SS). I have served as President of the Immunotoxicology, Metals and Ethical, Legal, Forensic and Societal Issues Specialty Section and currently serve as Senior Councilor of the Inhalation and Respiratory Specialty Section. I have received three major SOT awards including the Mentorship Award from "Women in Toxicology", Global Host award and in 2018, Education award for meritorious teaching skills in toxicology. As a teaching scholar, I have taught and continue to teach toxicology on a global level in such countries as Thailand, Nigeria, South Africa, Tasmania and New Zealand.

My education, training and publications are further set out in my Curriculum Vitae, which is attached to this report as an **Exhibit A**.

II. MANDATE AND METHODOLOGY

Mandate: I was asked to review the scientific literature and assess whether there is a biologically plausible explanation for the increased risk of ovarian cancer with the perineal use of talcum powder products.

The notion of biological plausibility is multi-factoral. As a part of my analysis, while considering the totality of the evidence, I evaluated the genital use of talcum powder products, the routes of exposure by which talcum powder could reach the ovaries, the composition of the talcum powder products, the biological and toxicological effects of talcum powder, and the potential mechanisms of carciogenisis. Biological plausibility does not mean proof of mechanism, but rather whether what is known about the products is consistent with a cause and effect relationship.

I performed an independent, comprehensive literature review using research databases and search engines including PubMed, ToxLit and Google to identify relevant literature. The keywords/phrases used initially for searching, included: talc, talcum powder, talc and cancer, talc and toxicity, talc and toxicology, ovarian cancer, oxidative stress, talc and ovarian cancer, animal models and talc, talc powder and the immune response and talc chemical structure. Keywords and phrases expanded upon those terms in later searches.

More than 300 publications (research papers, reviews, abstracts, reports, documents) and book chapters from the 1960s to the present were identified as having some relevancy for the talc-ovarian cancer topic. Following closer scrutiny of these publications, between 200-250 research papers, scholarly reviews, abstracts, documents, reports were found critical for informing my opinion. Toxicological studies, including *in vivo, in vitro* and *ex vivo* investigations, were the topics most appropriate for my area of expertise. In addition, I have reviewed depositions and numerous documents, internal memorandum

and published and unpublished studies and testing results that I have found in my own searches, documents provided by attorneys, and documents that I requested. A list of materials and data considered for this report are attached as **Exhitit B**.

My opinions below are based upon my experience as a toxicologist and research scientist and have been reached through employing the same scientific methodology and rigor that I employ in my academic research and professional duties. To my knowledge, I considered and evaluated the majority of all available relevant studies in the process of evaluating the literature, including those that reported an elevated risk of ovarian cancer with exposure to talc and those where other chemicals were reported within talc-based body powders, including those that did not find an increased risk. The same approach was used in evaluating the animal data and the mechanistic data.

III. TALC

Primary talc deposits are found on almost every continent around the world [1]. Talc is commonly formed by the hydrothermal alteration of magnesium- and iron-rich rocks (ultramafic rocks) and by low-grade thermal metamorphism of siliceous dolomites. Talc is the softest mineral on earth, mined around the world for use in a wide variety of products personal, cosmetic or industrial in nature. The word "talc" can refer to two things. The first is a mineral and the second is a commercially available product that can be used both industrially and in pharmaceuticals and cosmetics. For this report, when talking about the former, I use the term "mineral talc," and when talking about the latter, I use the term "talcum powder products." Johnson & Johnson talcum powder products are classified as cosmetic talc. Dermal contact (including perineal application of talcum powder products) is a primary route of human exposure, while inhalation also represents a route of exposure for talc/talcum powder products.

As a mineral, talc corresponds to the chemical structure of hydrous magnesium silicate with a formula of $Mg_3Si_4O_{10}(OH)_2$ and a theoretical chemical composition, expressed as oxides, of 31.7% by weight magnesium oxide (MgO), 63.5% silicon dioxide (SiO_2) and 4.8% water (H_2O). Talc belongs to the silicate subclass phyllosilicates and is known as a sheet silicate. It is the softest mineral on Mohs' hardness scale, and it's structure and chemical bond arrangement is such that it is easily broken into thin sheets. The structure consists of three sheets that are octahedrally coordinated magnesium hydroxide groups (brucite layer) layered between 2 layers of tetrahedrally linked silica layers. The apical oxygen atom positions of the tetrahedral layers are shared with one of the oxygen atom positions of the octahedral layer. The composite sheets repeat every 9.4 angstroms and the triple-sheet crystalline units are held together by van der Waals forces. Talc particles are normally plate-like in shape, but may form mineral fibers, as discussed below.

[1] https://minerals.usgs.gov/minerals/pubs/commodity/talc/mcs-2017-talc.pdf

Small amounts of aluminum and ferric (III) iron can substitute for silicon in talc tetrahedral sites. Trace amounts of nickel and small to moderate amounts of ferrous (II) and ferric (III) iron, aluminum and/or manganese can substitute for magnesium in talc octahedral sites. Additionally, talc deposits may contain varying amounts of quartz, nickel, chromium and cobalt, as well as asbestos or asbestos-forming minerals including amphibole (tremolite, actinolite, antigorite and anthophyllite) and serpentine (chrysotile) (Cralley, 1968; Lockey, 1981; McCarthy 2006; Rohl, 1976). The pH of cosmetic talcs are usually alkaline (8.0-9.5) and are insoluble in water, cold acids or in alkalis.

Talc powder particle size depends on the process used to make the powder. Johnson and Johnson's analysis of particle size in talcum powder shows particles range on average from 0.8 µm to over 50 µm, with a median particle size of 11.39 µm, where approximately 43.9% of particles are less than 10 µm (JNJTALC00878141).

A. Fibrous Talc

As a mineral, talc is most commonly found in plate-like form, but may also form as true mineral fibers that are asbestiform (IARC 2010, IARC 2012). Asbestiform talc (also known as fibrous talc) is different from talc containing asbestos. Fibrous talc fibers are very long and thin and occur in parallel bundles that are easily separated from each other by hand pressure (IARC Monographs, 2010). The 2010 IARC clearly states that the term 'asbestiform fiber' means any mineral, including talc, when it grows into an asbestiform habit. In its fibrous form, talc has been classified as a Group I, known carcinogen (IARC 1987 Supp 7; IARC 2010; IARC 2012). OSHA considered fibrous talc exposure limits to be equivalent to those of asbestos (OSHA, 1972). In 2010, IARC expanded the Group 1 designation ("known carcinogen") from "talc containing asbestiform fibers" to "talc containing asbestos or other asbestiform fibres." (IARC, 2010). Additionally, the American Conference of Governmental Industrial Hygienists (ACGIH) clarifies that "talc may also take the form of long thin fibers (fibrous talc) and can occur in bundles that are easily separated (asbestiform talc). Asbestiform talc should not be confused with talc containing asbestos…" (ACGIH, 2010).

Asbestiform talc fibers have been reported by Johnson & Johnson and Imerys to be found in: mines from which ore for Johnson & Johnson talcum powder products were sourced; in talcum powder used in Johnson & Johnson talcum powder products; and in the Johnson & Johnson talcum powder final product.[2]

Recent TEM testing on historic samples of Johnson's Baby Powder from 1978 showed the presence of fibrous talc in the product (Longo & Rigler, Feb 2018 MAS Report). Additional TEM testing of 30 samples of J & J baby powder and Shower to Shower dating from a span of many years resulted in a finding of fibrous talc in 15 samples (Longo & Rigler, Aug 2017 Expert Report).

[2] See also: IMERYS477879 (fibrous talc in Grade 66 Q1 composite); JNJ 000269848 (talc needles found in medicated powder 1971, see with TEM results in JNJ 000281921); JNJ 000245002 (Fibrous talc in Hammondsville mine 1970)) .

IV. ASBESTOS

Asbestos, like talc, is a naturally occurring silicate mineral, but with a different crystal structure (Mossman & Churg, 1998). Asbestos is a generic name referring to a group of naturally occurring mineral silicate fibers. It is recognized as a known human carcinogen by the U.S. Occupational Safety and Health Administration (OSHA), the U.S. Environmental Protection Agency (USEPA) and the National Toxicology Program (NTP)(OSHA, 2014; USEPA, 1995; NTP, 2016). The National Institute for Occupational Health (NIOSH) has stated there is no safe level of asbestos and the American Conference of Governmental Industrial Hygienists (ACGIH) characterizes it as a "confirmed human carcinogen" (NIOSH, 1980; ACGIH, 2017). All forms of asbestos are Group 1 carcinogens (carcinogenic to humans)(IARC, 2012).

The U.S. EPA defines asbestos by limiting the term to 6 specific fibrous minerals from two distinct groups: chrysotile (from the Serpentine group); and amosite, crocidolite, tremolite, actinolite and anthophyllite (from the Amphibole group). "Asbestiform" describes the pattern of growth of a mineral that is referred to as a "habit" (IARC, 2010). Minerals with a "non-asbestiform" habit have crystals that grow in two or three dimensions, and "cleave into fragments, rather than breaking into fibrils" (*Id.*). Chrysotile occurs in the asbestiform habit, whereas, of the amphiboles, amosite and crocidolite occur only in the asbestiform habit, and tremolite, anthophyllite and actinolyte can occur in asbestiform or non-asbestiform habits. OSHA defines an asbestos fiber as having a length > 5mm and a length:width aspect ratio of 3:1, whereas the USEPA definitition incorporates the aspect ratio of > 5:1 (OSHA, 1992; USEPA, 1987).

While amphibole and serpentine asbestos may have fibrous habits, they have very different forms. The amphiboles are double-chain silicates also called inosilicates. The basic structural unit is $(Si_4O_{11})^{-6}$ with side groups that are responsible for the overall amphibole structure. Amphiboles are distinguished from one another by the amount and positioning of metal atoms including: sodium, calcium, manganese, magnesium, iron(II), iron(III) and aluminum. Traces of these types of asbestos are extracted when other minerals are being mined and, due to inefficient or non-existant separation techniques, are ultimately incorporated into the final product. Even incidental contamination by amphibole forms of asbestos is hazardous enough to cause asbestos-related illnesses (Rohl & Langer, 1976).

The serpentine group of minerals has the formula $Mg_3Si_2O_5(OH)_4$ and the structure resembles a bending sheet. Chrysotile is the only one in which the sheets are bent to form continuous tubes, which gives the mineral the fibrous habit related to asbestos. Chrysotile is very flexible and less likely to be "friable" than the amphiboles. Friability of asbestos is generally defined as the ability to easily be turned into a dust with finger pressure. It is this friability that can release asbestos fibers and potentially result in health problems.

A. Asbestos in Talc

Associated minerals found in commercial talc products vary from deposit to deposit depending on the formation conditions. The most common minerals associated with talc include chlorite, magnetite, dolomite, calcite, mica, quartz and fluoapatite (Fiume et al., 2015). In its natural form, some talc also contains asbestos, classified as a Group I, "known carcinogen" by IARC (IARC Monographs, 1973, 1977, 1987, 2012). Amphiboles and serpentine fibers have been associated with many talc deposits (Van Gosen, 2004; Marconi and Verdel, 1990; Lockey, 1981; Rohl and Langer, 1974; Gamble et al., 1979; Kleinfeld et al., 1973, 1974; Pooley, 1972 (JNJ000319762); Chidester, 1968). The close proximity of asbestos and talc in mineral deposits makes extraction of either material alone difficult, if not impossible. (Rohl and Langer, 1974; IARC, 2010; Dion et al. 2010[3]).

Cralley (1968) analyzed twenty-two commercially available cosmetic talcum products (manufacturers not reported). Authors reported the fiber content ranged from 8% - 30% (by count) with an average of 19% and that the fibrous material was predominantly fibrous talc. Pooley and Rowlands (1975) analyzed twenty-seven talc powders (cosmetic and industrial) and detected tremolite fibers in three samples.

Because asbestos is a known carcinogen, its presence in cosmetic talc is unacceptable (FDA, 2012; FDA 2015). The former Director of National Institute for Occupational Safety and Health (NIOSH) and former President of Industrial Minerals Association – North America (IMA-NA) stated in a recent deposition that if there were a fiber of asbestos in talcum-based products it would "certainly" provide a biologically plausible mechanism for increased lung disease, and that he suspected it would also have a "similar mechanism of disease in other tissues and organs" (Deposition of Robert Glenn, October 18, 2018, 341:15-342:3).

In 1976, specifications were developed for cosmetic talc requiring that no detectable fibrous, asbestos mineral be present (CTFA, 1990; Fiume, 2015). The talc industry, and specifically Defendants, developed a "zero tolerance" standard for asbestos in talc (IMERYS 170006; JNJ 000383662; JNJ 000001918). Despite this standard, the presence of asbestos in cosmetic talc has been reported in the literature, and Johnsom and Johnson indicated in a letter in 1973 that "asbestos-form particles cannot be removed from talc" and that the "Johnson & Johnson process for beneficiating Vermont talc…will not guarantee a zero tolerance for elongated particles" (JNJ 000233691). In 1976, Rohl et al. tested 20 different talcs and powders including 20 body powders, baby powders, facial talcums, and also one pharmaceutical talc to determine their mineralogical and chemical composition. Where known, all were formulated prior to 1973. Of the 20 products, 9 contained detectable amounts of tremolite and anthophyllite, principally asbestiform, while some also contained fragmented forms of these minerals. The amounts ranged from tenths of a percent to over 14% by weight; two contained detectable amounts of chrysotile asbestos fiber. Eight samples contained quartz, seven ranging from 2 to 5%, with one as high as 35%. Analyses showed that the consumer products examined were rarely the pure mineral talc, but rather were mixtures of various minerals.

[3] Available online at: http://www.irsst.qc.ca/media/documents/PubIRSST/R-755.pdf

In 1984, Paoletti et al. performed studies by electron microscopy to assess asbestos contamination in industrial and cosmetic talcs from the Italian market and the European Pharmacopoeia (Paoletti, 1984). Nine of the 25 pharmaceutical and cosmetic grade talcs contained tremolite fibers, with total percent asbestos concentrations ranging from 0.4% - 22%. About half of the talc powders revealed the presence of asbestos: in five samples chrysotile (a serpentine asbestos) was present, the others contained tremolite and anthophyllite (an amphibole asbestos).

Cosmetic and pharmaceutical talc products from deposits in Vermont, Montana, North Carolina and Alabama were examined and tested positive for asbestos (Blount, 1991). The investigator of that study recently affirmed the samples included Johnson & Johnson baby powder, purchased off the shelf (Deposition of Alice Blount, PhD, April 13, 2018). The early analytical methods used to measure asbestos fibers before 1990 were not very sensitive and thus it appears that extrapolation of the levels of asbestos from counts measured before this date could have been conservative (Blount, 1991).

In a study that examined the amphibole asbestos content of commercial talc deposits in the USA, Van Gosen et al. (2004) found that the talc-forming environment directly influenced the amphibole and amphibole-asbestos content of the talc deposit. Specifically, the study found that contact metamorphic talcs showed a strong tendency to contain amphiboles, and regional metamorphic talc bodies consistently contained amphiboles, which display a variety of compositions and habits (including asbestiform). In a German study (Mattenklott, 2007), the author examined the presence of asbestos in talc powder and found that in one-quarter of the 57 talc powder samples tested, asbestos could be detected. Two samples contained quantities exceeding 0.1 weight percent which could reach a value of 10,000 fibers/m^3. This weight percent is, in some cases, half that reported by Johnson & Johnson in their internal documents, as seen in the corporate depositions reported below.

Defendants have claimed that asbestos has been "eliminated" from cosmetic talc products.[4] However, there is substantial evidence that talcum powder products still contain asbestos, recognized as a Group 1 carcinogen. During the recent deposition of John Hopkins (Johnson and Johnson corporate representative), Mr. Hopkins affirmed testing results showing the presence of asbestos in mines from which talc ore was taken for use in Johnson & Johnson baby powder products, processed talc used in Johnson & Johnson baby powder products, and in complete Johnson & Johnson baby powder products. Those results may be found at Exhibit 28[5] of Dr. Hopkins' deposition. Additional examples of testing performed by and commissioned by Johnson and Johnson and Imerys may be found at Exhibit 47 to the deposition of Julie Pier, corporate representative of Imerys.[6]

In 1975, McCrone Associates also confirmed the presence of amphibole particles, alone and in bundles as seen in Defendants' internal documents (JNJMX68_000012745). In 2004, a television station reported that Johnson's Baby Powder had been analyzed and found anthophyllite asbestos at 0.2% (JNJ 000089413). A 1972 Johnson & Johnson document demonstrates the presence of up to 5% chrysotile in

[4] PCPC Submission to FDA, July 2009 – "Since the early 1970's, the relevant industries voluntarily eliminated asbestos contamination from talc products."
[5] Ex. 28, John Hopkins Dep. (Aug. 16 & 17, 2018; Oct. 17, 2018; and Nov. 5, 2018).
[6] Ex. 47, Julie Pier Dep. (Sept. 12 & 13, 2018).

Johnson's Baby Powder and Shower to Shower samples (JNJ 000232996). These data clearly demonstrate the possibility for women who used talcum powder during these dates to have had exposure to this ovarian carcinogen.

Recent TEM testing on historic samples of Johnson & Johnson baby powder from 1978 showed the presence of fibrous anthophyllite in the product. (Longo and Rigler, 2018; Ex. 47, Pier Dep.). Additional TEM testing of 30 samples of Johnson & Johnson baby powder and Shower to Shower ranging in production date over a span of many years resulted in a finding of amphibole asbestos (tremolite, anthophyllite, richterite and actinolite) in 17 samples. (Longo and Rigler, 2017). Additionally, I have reviewed a recent report prepared by Dr. William Longo and Dr. Mark Rigler that reports that talcum powder products manufactured by Johnson & Johnson's Baby Powder and Shower to Shower have contained and continue to contain asbestos and talc containing asbestiform fibers (e.g. talc occurring in a fibrous habit).[7] These results were obtained from testing talcum powder product samples manufactured during the period of the 1960s through the 1990s. Results showed 37 of 56 samples tested contained tremolite and/or anthophyllite asbestos, and 41 of 42 samples tested contained fibrous talc.

The substantial evidence of the presence of asbestos and fibrous talc in talcum powder products provides a biologically plausible explanation for the increased risk of ovarian cancer associated with the perineal use of talcum powder products.

V. HEAVY METALS

A. Properties of Heavy Metals

Nickel is classified by IARC as a human carcinogen (Group 1) (IARC, 1973, 1976, 1979, 1982, 1987, 1990). The exact mechanisms of nickel-induced carcinogenesis are not known, but likely involve genetic and epigenetic routes. Nickel (II)-induced genotoxicity may be aggravated through the generation of DNA-damaging reactive oxygen species (ROS) and the inhibition of DNA repair by this metal. Nickel exposure also causes a broad spectrum of epigenetic effects. Contact with nickel compounds can cause a variety of adverse effects on human health (Zambelli and Ciurli, 2013).

Nickel ions have been shown to cause single-strand DNA breaks and DNA-protein crosslinks (Patierno, 1985). In a study by Patierno (1985), Chinese hamster ovary cells were exposed to $NiCl_2$, and nickel-induced DA-protein crosslinking appeared in late S phase of the cell cycle (*Id.*). Authors associate these alterations as an early event in the process of nickel transformation (*Id.*).

Contact with nickel compounds can cause a variety of adverse effects on human health, such as nickel allergy in the form of contact dermatitis, lung fibrosis, cardiovascular and kidney diseases and

[7] Expert Report of William E. Longo, PhD and Mark W. Rigler, PhD (Nov. 14, 2018).

cancer of the respiratory tract. Chronic non-cancer health effects may result from long-term exposure to relatively low concentrations of pollutants (Duda-Chodak and Blaszcyk, 2008). Although the accumulation of nickel in the body through chronic exposure can lead to a number of diseases, the most serious concerns relate to nickel's carcinogenic activity. Increased risks of malignant tumors, such as nasal and sinusoidal cancers, and cancers of the lung and larynx have been noted (IARC, 1987). The marked differences in the carcinogenic activities of various nickel compounds most likely reflect the differences in their uptake, transport, distribution and retention, and ultimately—the capacity to deliver nickel (II) ions to specific cells and target molecules.

In experimental animals, nickel compounds induce tumors at virtually all sites of application (Denkhaus, 2002; IARC, 1987; Zabmelli, 2013). The routes of administration that were shown to produce tumors include inhalation, intramuscular, intrarenal, intraperitoneal, intraocular, subcutaneous and the intra-articular space (*Id.*).

Chromium is a naturally occurring element found in rocks, animals, plants, soil, and volcanic dust and gases. It comes in several different forms, including trivalent chromium (chromium (III)) and hexavalent chromium (chromium (VI)). In contrast, chromium (VI) compounds cause cancer in humans and in experimental animals and exert genetic toxicity in bacteria and in mammalian cells *in vitro* (Fang, 2014; IARC, 2009). Adverse health effects, other than cancer, associated with chromium (VI) exposure include occupational asthma, eye irritation and damage, perforated eardrums, respiratory irritation, kidney damage, liver damage, pulmonary congestion and edema, upper abdominal pain, nose irritation and damage, respiratory cancer, skin irritation, and erosion and discoloration of the teeth. Some people with extensive dermal exposure can also develop an allergic skin reaction, called allergic contact dermatitis (Bruynzeel et al., 1988). Primary irritant dermatitis is related to the direct cytotoxic properties of chromium, while allergic contact dermatitis is an inflammatory response mediated by the immune system. During reduction to the trivalent form, chromium may interact with cellular macromolecules, including DNA (Wiegand et al., 1985), or may be slowly released from the cell. Complexes of chromium (III) that are bound to lower molecular weight ligands are most likely to be able to traverse cell membranes.

Chromium (III) has weak cell membrane permeability, allowing it to cross the cell membrane, where it can bind to DNA and cause lesions, resulting in genetic damage such as strand breaks and DNA-protein crosslinks (Nickens, 2010). This damage leads to genomic instability. Another study has shown that chromium (III) causes DNA damage in cells by interfering with base pair stacking in the cell's replication cycle, and chromium (VI) intercalates DNA – both directly cause genotoxicity in vivo (Fang, 2014).

Hexavalent chromium compounds are classified by IARC as carcinogenic to humans (Group 1)(IARC, 2009). Mechanistically, they have been shown to cause direct DNA damage after intracellular reduction to Cr(III), mutation, genomic inistability, aneuploidy, and cell transformation (*Id.*). Chromium (VI) can cause damage leading to dysfunctional DNA replication, aberrant cell cycle, DNA strand breaks, dysfunctional DNA repair and DNA-protein crosslinks and directly causing genotoxicity (Nickens, 2010).

Besides direct genotoxic effects of chromium (VI), chromium compounds such as chromate can activate transcription factors involved in inflammation and tumor growth (IARC, 1990). Major factors

governing the toxicity of chromium compounds are oxidation state and solubility. These compounds, which are powerful oxidizing agents and thus tend to be irritating and corrosive, appear to be much more toxic systemically than chromium (III) compounds, given similar amounts and solubilities. Chromium (VI) enters many types of cells and, under physiological conditions, can be reduced by hydrogen peroxide (H_2O_2), glutathione (GSH) reductase and ascorbic acid to produce reactive intermediates, including chromium (V), chromium (IV), thiyl radicals, hydroxyl radicals, and ultimately, chromium (III). Any of these species could attack DNA, proteins and membrane lipids, thereby disrupting cellular integrity and functions (De Mattia, Bravi *et al.* 2004). Besides cancer, chromium is one of the most common skin sensitizers. It also causes toxicity of the kidney, liver, gastrointestinal tract, and cardiovascular, hematological and reproductive systems along with causing developmental effects.[8] High doses of chromium (VI) compounds have been reported to cause developmental toxicity in mice and shown to potentiate the effects of other toxicants, including the nephrotoxins, mercuric chloride, citrinin, hexachlorobutadiene, and maleic acid.

Cobalt IARC declared that cobalt metal with tungsten carbide is *probably carcinogenic to humans (Group 2A)*, while cobalt metal without tungsten carbide is *possibly carcinogenic to humans (Group 2B)*. Two different mechanisms of genotoxicity, (1) DNA breakage induced by cobalt metal and especially hard metal particles, and (2) inhibition of DNA repair by cobalt (II) ions contribute to the carcinogenic potential of cobalt compounds (Lison et al., 2001; IARC, 2006). Cobalt can also contribute to allergic reactions. In humans, gastrointestinal absorption of cobalt has been reported to vary between 5 and 45% and it has been suggested that absorption is higher in women than in men. Cobalt can be absorbed through intact human skin (IARC, 2006). Soluble cobalt salts interfere adversely with cell division, bind irreversibly to nucleic acids in the cell nucleus, induce chromosome aberrations in plants, and are weakly mutagenic in some *in vitro* tests. Injections or implantation of cobalt metal, alloys and compounds induced local and sometimes metastasizing sarcomas in rats, rabbits, and mice (*Id.*). Data indicating possible carcinogenic effects of cobalt alloys or compounds in human populations has arisen from medical use, use in hard-metal industries, and from cobalt production sites.

B. Metals in Talcum Powder Products

In an early paper by Cralley et al., (1968), 22 cosmetic talcum products purchased off the shelf were analyzed for fibrous content, selected metals and quartz. In these studies, 19 samples contained cobalt under 25 parts per million (ppm) by weight, chromium under 22 ppm, nickel below 29 ppm and manganese under 78 ppm. Certain samples had a nickel content of 1270 ppm, chromium 340 ppm and 1210 ppm nickel; qualitative tests demonstrated that some of the chromium was hexavalent (carcinogenic form). All of these talcs had a considerable fiber content (suggesting the presence of asbestos) (*Id.*). Studies here suggest that women who used talcum powder in the 1960s could have been exposed to considerable amounts of toxic heavy metals depending on the type of talc used and frequency of use (*Id.*).

[8] Accessible online at: https://www.atsdr.cdc.gov/csem/csem.asp?csem=10&po=10

In a 2013 study by Rehman, toxic and carcinogenic heavy metals were found to be present in small amounts in all 30 brands of cosmetic talcum powder tested; the concentrations of heavy metals differed dramatically depending upon the brand of talcum powder (Rehman, 2013). Heavy metals measured (and found in samples) included cadmium, chromium, copper, cobalt and lead. Authors found all levels to be within safe limits. However, authors caution that excess use of talcum powder affects the health of the consumer (*Id.*).

In a paper by Gondal et al. (2012), published in Applied Optics, lead and chromium were measured in talcum powder using laser-breakdown spectroscopy. Using this system, the authors were able to detect 15-20 parts per million (ppm) of lead and 20-30 ppm of total chromium in the talcum powder sample. This study, like that by Rehman, demonstrates the presence of toxic heavy metals associated with talcum powder. However, the levels of heavy metals in this study were significantly higher. The method used for measuring metals in this study was far more precise than that used by Rehman et al. (2013). This study supports the presence of toxic and potentially carcinogenic metals in some talcum powders.

According to Johnson & Johnson's corporate representative, the maximum amount of allowable nickel in the company's talcum powder products was 5 ppm (Deposition of John Hopkins, August 16, 2018, Ex. 3). Written specifications state that the maximum allowable nickel content is 10 ppm (JNJ 000629320; JNJ000488188; JNJMX68_000022920). Despite these limits, nickel in concentrations exceeding 2000 ppm were reported in Vermont talc used in talcum powder products for decades, greatly in excess of the product specification limit of 10 ppm (JNJ 000629320; JNJ 000488188; JNJMX68_000022920). Examples of testing results for heavy metals in Defendants' talcum powder products can be found in **Exhibit C**, attached to this report.

Over the years from 1972 to 2004, talc mined in Vermont had consistent, excessive levels of nickel, routinely exceeding 94 to 250 times the upper limit provided in J&J's specifications (Exhibit C). This is troubling considering nickel is a known carcinogen (IARC 2012).

Cobalt was found in Vermont talc ores in amounts ranging from 8 – 89 ppm from 1972 through 2004. Like nickel it, too, appears to occur routinely in talc products in amounts exceeding the 10 ppm upper limit for heavy metals in the talc product specifications (Exhibit C).

Internal documents outline Johnson & Johnson's concern regarding the potential carcinogenic nature of chromium (VI), a Group I carcinogen (JNJ 000131758; JNJ 000131754; JNJ 000378044; JNJ 000378046). A 2010 J&J memo written discusses raising the upper limit acceptable for total Cr to 7 ppm (JNJ 000131758). An accompanying memo also discusses the relationship between chromium (III) and chromium (VI) (JNJ 000131754), and a discussion of the inhalation of hexavalent chromium is contained in this document. Regardless of valence, Grade 66 analyses consistently show total chromium contents far in excess of 5-, 7-, or 10 ppm. During the period from 1972 thru 2004, the chromium content varied from 25 ppm to 569 ppm (Ex. 47, Pier Dep.), with typical levels around 200 ppm.

Interestingly, there is a significant difference between the reported chromium content of Grade 66 talc when the sample has been prepared by Johnson & Johnson (internal) method BPT 148 versus the

United States Pharmacopeia (USP) method which uses a total digestion technique (IMERYS-A_0015621). The levels reported using the USP method were much higher than the Johnson & Johnson method (*Id.*).

C. Fragrances

There are more than 150 different chemicals added to Johnson's Baby Powder and Shower to Shower products. I reviewed the expert report from Dr. Michael Crowley that concludes that some of these chemicals may contribute to the inflammatory response, toxicity, and potential carcinogenicity of Johnson & Johnson's talcum powder products.[9] I concur with his opinion.

There is substantial evidence that talcum powder products contain excess levels of nickel, chromium, and cobalt, all known carcinogens and/or inflammatory agents. Moreover, a significant number of the fragrance chemicals added to talc elicit an inflammatory response. Each of these elements individually and together can contribute to an inflammatory response caused by the product. As will be explained in more detail below, inflammation is a known mediator of ovarian cancer. The presence of these inflammatory agents provides additional biologic evidence explaining the causal relationship between genital use of talc and ovarian cancer.

VI. EXPOSURE – TALC PARTICLE ACCESS TO THE BODY

A. Exposure Routes

Based on the tenets of toxicology, there are four basic routes of human exposure including: inhalation, ingestion, dermal and injection.

A common exposure route for cosmetic talc is via the dermal route, including vaginally after perineal application. Talc body powders are often applied to the perineum for hygienic purposes. It has been shown that glove powder and other materials can migrate upwards through the female reproductive tract (Venter & Iturralde, 1979; Iturre and Venter, 1981; Sjosten et al., 2004; Heller et al., 1995) and the data are supported by animal investigations (Wright et al., 1996; Edelstam et al., 1997; De Boer, 1972; Henderson et al., 1986), also reflective of a dermal exposure route.

Inhalation is the route of exposure that has been most commonly studied to assess talc toxicity. In one inhalation study, after talc exposure of hamsters, there was a consistent elevation in cytotoxic enzyme levels, and macrophage phagocytosis was persistently depressed (Beck et al., 1987). These results also indicated that, when a similar mass of talc and granite dust (12% quartz) was deposited in the lungs,

[9] Expert Report of Michael Crowley, PhD (Nov. 12, 2018).

talc caused more lung injury than did granite (*Id.*). Based on its physical properties talc, in a powder form, can be inhaled while being applied (EPA, 1992; IARC, 2010). Additional evidence that application of talc body powder products results in inhalation exposure of talcum powder is provided in a 2017 study by Longo, et. al., and other studies (Longo, September 2017, "*Below the Waist Application of Johnson & Johnson Baby Powder*"; Wells, 1979; van Huisstede, 2010; Frank and Jorge, 2011; Jasuja, 2017).

1. Dermal - Migration Through the Upper Genital Tract

Animal models: Though animal studies have limitations due to the differences in anatomy, they provide evidence that talc can migrate through the reproductive system. Rats were exposed vaginally or via the perineum to either talc or no treatment for 3-mo on a daily basis (Keskin et al., 2009). In this study, there was evidence of foreign body reaction and genital infection, along with an increase in inflammatory cells in all the genital tissues. While no neoplastic changes were observed, the number of ovarian follicles in the talc groups were increased. No peritoneal changes were observed. The investigators concluded that talc by perineum exposure has adverse effects on the genital system in the form of foreign body reactions and infection (*Id.*).

In a series of two experiments, Henderson et al. (1986) demonstrated the presence of talc in the ovaries of two groups of animals following vaginal and intrauterine talc applications, whereas none was present in the ovaries of control animals. Particles were also seen in animals that had received intravaginal talc that were sacrificed after 4 days. (*Id.*)

Studies by Wright et al. (1995) also demonstrated the potential toxicity of retrograde uterine passage of particulate matter. Despite the aforementioned studies which demonstrate the plausibility of talc translocation, a study by Wehner et al. (1996) failed to demonstrate the same outcomes in a small sample of monkeys, which may have been due to the small sample size.

Human studies: A number of human studies over many years have observed migration of particles following vaginal administration: these studies began as early as 1961 when Egli and Newton studied the translocation of carbon particles following vagina application. In 1972, De Boer deposited colloidal carbon black (CB) suspension in the uterus, cervical canal or vagina in over 100 patients prior to surgery (De Boer, 1972). Subsequent observation revealed rapid translocation of CB to the oviducts and beyond. Some CB deposited in the cervical canal also translocated to the uterine passage, albeit in a lower percentage of patients (*Id.*). An early study by the National Institute of Occupational Safety and Health (NIOSH) in 1972 showed commercially available talc body powder samples contained fibers, and that exposure to fibers occurred during diapering (JNJ 000231304).

A study by Venter and Itteralde (1979) administered radiolabeled human albumin microspheres (no size provided) in the vagina of patients, followed by surgical removal of uterus, oviducts and ovaries. Results demonstrated that 9 out of 14 patients had radioactivity in their oviducts and ovaries. Recent studies have demonstrated the presence of talc particles in ovarian tumors (to be discussed in a later section). Another clinical study examined a total of 24 women undergoing oopherectormy (Heller et al.,

1995). In this case, women were questioned as to their use of perineal talc applications. Ovarian tissue was removed from each group and analyzed and quantitated for talc by polarized light and electron microscopy. These data support the ability of talc to migrate from the perineal region upward and reach the upper genital tract (*Id.*).

Further evidence for migration of particles to the upper genital areas comes from a document from the FDA to Dr. Epstein (Cancer Prevention Coalition, University of Illinois, Chicago) concerning Citizen Petitions dated 1994 and 2008 and requesting a cancer warning on cosmetic talc products. In this document, the FDA stated that “the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable” (JNJ 000488318).

In addition, a 2004 document from Luzenac America to Dr. Al Wehner (IMERYS 137677) recalls a 2004 published paper by Sjosten et al. (2004). Luzenac states that the paper “offers some compelling evidence **in support** of the ‘migration’ hypothesis.” The paper concluded that starch particles migrate from the vagina through the Fallopian tubes up to four days after examination with powdered gloves (*Id.*). The author of the Luzenac document goes on to state that combining this evidence with the theory that talc inititates epithelial inflammation and you have a “potential formula” for the NTP classification of talc as a carcinogen.

The most recent systematic review of the association between genital use of talcum powder products and ovarian cancer (Penninkilampi, 2018) reported an increased risk of ovarian cancer with increased perineal talcum powder use, with a slightly higher risk in women who report greater usage. Data was collected as “lifetime” usage – frequency of use over time. Any use was associated with increased risk of ovarian cancer as compared to no use, and women with long-term (> 10 years) talcum powder use had an increased risk. The authors concluded perineal talcum powder use and ovarian cancer were consistently associated, with a slightly higher risk in women who report greater usage.

Pathways that allow for the migration of particles to the lymph nodes are also available for that complex portion of the lymphatic system surrounding the ovaries. Importantly, studies by Chan et al. (2007) have demonstrated a positive association between lymphadenectomy and survival in stage 1 ovarian cancer patients. In support of this finding, Cramer et al. (2007) described the presence of talc particles in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc.

Animal and human studies demonstrate that talcum powder products can migrate from the perineal region to the ovaries.

2. Inhalation

Effects of size on particle translocation and toxicity have been studied most extensively with inhaled particulate air pollutants and nanomaterials. These studies will be discussed to provide a scientific

premise for movement of particles of a certain size throughout the body. Small-sized particles can enter the bloodstream – translocation of particles and often toxicity are related to their size; perhaps because of the larger mass concentration of smaller vs. larger particles (Driscoll et al., 1997).
J&J's analysis of particle size in talcum powder products shows particles range on average from 0.8 µm to over 50 µm, with a median particle size of 11.39 µm, where approximately 43.9% of particles are less than 10 µm (JNJTALC00878141).

Ultrafine particles (UFPs; < 0.1 µm) can directly affect the cardiovascular system by migration from the respiratory system to the systemic circulation (Nakane, 2012; Elder et al., 2006; Kreyling et al., 2006). Inhaled UFPs deposited in the lung can pass through the epithelial barrier because of their very small size; some particles may move into lung capillaries and then into the systemic circulation. Numerous studies and reviews have been written concerning the migration of these particles. In a systematic literature review (Nakane, 2012), particle size was shown to be a strong factor for migration. Particles that were translocated to various sites were observed to have the following sizes: ≤0.05 µm for remote organs, ≤1 µm for blood, and ≤10 µm for lung tissues. In order to be detected in the blood, particles that have passed through the epithelial barrier of the lungs must migrate into the capillaries. The largest chance for migration to the brain was observed at a 0.05-µm cutoff size. However, MnO_2 particles as large as 1.3 µm have also been detected in the cerebral cortex (Nakane, 2012). A categorical regression analysis based on currently available inhalation data showed that all of the effects of particle size, particle material, animal species, and exposure route were statistically significant (*Id.*). The effects were large for particle size and particle material, and small for exposure route and animal species. These results suggest that, in an experiment to evaluate the migration of solid particles, the characteristics of the particles (i.e., size and material) should be considered carefully.

Evidence from an internal document (1971) demonstrates rolled talc fibers between 0.1 - 3µm in a Johnson and Johnson's commercial product (JNJAZ55_000005957). Other documents from Defendants have demonstrated that while median particle size is ~10.5 µm, sizes can be as small as 0.3 µm (IMERYS030347; IMERYS031791). V66 non-shear talc was approved for use in JNJ Shower to Showder products and the size of some of the particles had a diameter as small as 0.1 µm (JNJTALC000878141). While the median particle size was ~12 µm, the standard deviation was very high (~9µm) demonstrating a large range of particle sizes. Fine-size particles such as those found in talc, can also translocate readily throughout the body (Peters et al., 2006), providing a strong basis for the ability of fine-size talc particles (<2.5 µm to migrate throughout the body).

Ultrafine and fine particles can penetrate through the different tissue compartments of the lungs and eventually reach the capillaries and circulating cells. These particles are then translocated by the circulation to other organs including the liver, the spleen, the kidneys, the heart and the brain, and the ovaries where they may be deposited. It remains to be shown by which mechanism(s) ultrafine particles penetrate through tissue and enter capillaries. Lymph capillaries remove the large protein molecules and other particulate matter from the tissue spaces of the lung. Thus, cellular debris and foreign particles inhaled into the lungs can be conveyed to the regional lymph nodes.

Talc particle size analyses for many inhalation studies demonstrated that most talc particles were between 1 and 8 µm; 1 µm is considered ultrafine in size and thus particles could easily migrate from the lungs and throughout the body. Genofre et al., (2009) examined the effect of talc particle size on induced pleurodesis following intrapleural injection of rabbits with two different sizes of talc. One group contained mixed sizes of talc (mean size = 25.4 µm) and the other group small size talc only (mean size = 4.2 µm with 50% <6.4 µm) (*Id.*). Particles of both sizes migrated to the spleen, liver and kidney; more small talc particles (compared to mixed talc) was seen in the liver and kidneys. Both size particles produced an acute systemic inflammatory response, with small particle talc producing a more pronounced pleural and systemic response and resulting in greater particle deposition in the organs than the mixed talc (*Id.*). In addition, serum levels of the pro-inflammatory cytokine, IL-8 and VEGF were more markedly increased in the small talc group (*Id.*). Particles found in all systemic organs were <5µm. A number of other studies have shown migration of talc particles from the pleural cavity to the systemic circulation (Ferrer, 2002; Rossi, 2010). It appears that small particles may be more easily taken up by the lymphatics than larger particles. The inflammatory effects observed showed a strong correlation with the small particle group. This study shows that size of talc particles matter and the smaller the size the greater the ability to translocate and increase the extent of the inflammatory response. As Defendants' internal documents demonstrate their talc particle size to cover a wide size range (100 µm to ~0.3 µm).[10], there is extensive evidence that particles can be inhaled and transported through the blood and lymph to the ovaries.

In 1993, the National Toxicology Program (NTP) issued a report from a study concluding that there was "some evidence of carcinogenic activity" in male rats, "clear evidence of carcinogenic activity" in female rats, and no evidence of carcinogenic activity in male or female mice exposed to aersols of talc reported as nonasbestiform cosmetic-grade (National Toxicology Program, 1993). Authors of that study speculated these effects could be due to cytokines released from macrophages or a nonspecific effect of the stress of inflammation (*Id.*).

In another study, rabbits were injected with normal size talc (Dmax = 8.36 µm) or larger particles talc (Dmax = 12 µm) (Ferrer et al., 2002). Pleural inflammation was greater with normal talc than large talc, and animals receiving normal talc had talc particles in the liver, supporting the premise that talc particles instilled into the pleural cavity can escape and migrate to extrapleural organs. Talc dissemination can be significant, and granulomas have been seen to develop in the interstitium after particles migrate from the lungs, with resultant pulmonary interstitial fibrosis (Hollinger, 1990). In another study illustrating talc dissemination (Werebe, 1999), talc was administered into the pleural space of rats. At both 24- and 48-hours, talc crystals were found in every organ of all animals, with the amount of talc being statistically different between the organs. Authors concluded there was a rapid absorption of talc through the pleural surface and a progressive systemic distribution of particles (*Id.*).

In addition to migration of ultrafine particles through tissue and movement to the lymhph nodes, fine and coarse particles may be phagocytized by macrophages and dendritic cells which may carry the particles to lymph nodes in the lung or to those closely associated with the lungs (IARC, 2010). The uptake of fine particles (0.1–2.5 µm in diameter) by macrophages is a specific ligand-receptor mediated

[10] IMERYS346016; IMERYS030347; IMERYS031791; JNJAZ55_000005957.

actin-based process (phagocytosis), whereas the uptake of ultrafine particles (<0.1 µm in diameter) apparently occurs by other, non-specific mechanisms (Peters, 2006). These mechanisms are termed "adhesive interactions," and include electrostatic, van der Waals and steric inter-actions (*Id.*). Particles with a diameter of 0.2 µm and smaller appear to enter cells passively, that is by a mechanism which is different from phagocytosis. Larger particles are much more avidly taken up by macrophages, but by the specific receptor mediated, actin-dependent mechanism. Below the particle size of 0.2 µm, particles increasingly enter the macrophages by the non-specific "adhesive interaction" mechanisms mentioned above (*Id.*).

There is substantial evidence in the scientific and medical literature that support a conclusion that talc powder particles can reach the ovaries through inhalation.

VII. MECHANISM OF CANCER

A. Cancer - General

Tumorigenesis, the formation and growth of tumors, is a complex and multifactorial progressive process of transformation of normal cells into malignant ones (Pogribny and Rusyn, 2014). It is characterized by the accumulation of multiple cancer-specific heritable phenotypes, including persistent proliferative signaling, resistance to cell death, evasion of growth suppression, replicative immortality, inflammatory response, deregulation of energy metabolism, genomic instability, induction of angiogenesis, and activation of invasion ultimately resulting in metastases. It encompasses genetic, behavioral, and environmental factors that can all contribute to its development.

Mutations can occur as a result of the processes inside the cell, or alternatively, can be caused by external factors, such as chemicals. In addition, some people can inherit faults in particular genes that make them more likely to develop cancer. While normal cells obey signals indicating they have reached their growth limit, in cancer cells, the normal signaling system is disrupted. Mutations in particular genes may result in over- or under- production of proteins, or the production of abnormally formed proteins, all of which can lead to a lack of cellular regulation.

In general, cancer is an uncontrolled growth of abnormal cells in the body, which occurs when the body's normal control mechanisms are disrupted. Excessive cellular division leads to a growth called a tumor. Mutations can happen by chance when a cell is dividing. Some mutations act by inhibiting normal controls over cell growth, leading to uncontrolled cell division. DNA may be damaged during routine cellular processes, and cells have mechanisms to repair that damage. However, over time, the damage may accumulate. Once cells exhibit increased cell growth, they are more likely to pick up additional mutations and are less likely to be able to repair the damaged genes.

If the DNA damage cannot be repaired, the cell can self-destruct, a process called apoptosis. In cancer cells, molecules in the repair pathway are faulty. For example, a protein called p53 normally determines whether genes can be repaired or if the cell should undergo apoptosis. Many cancers have a defective version of p53, and don't repair themselves properly. Thus, cancer cells can override self-destruct signals and don't undergo apoptosis when they should.

B. Genetic Mutations

Inherited mutations are passed down from parent to child and are present throughout a person's life in virtually every cell in the body. These mutations are also called germline mutations because they are present in the parent's egg or sperm (germ) cells. When an egg and a sperm cell unite, the resulting fertilized egg cell receives DNA from both parents. If this DNA has a mutation, the child that grows from the fertilized egg will have the mutation in each of his or her cells.

A genetic predisposition (sometimes also called genetic susceptibility) is an increased likelihood of developing a particular disease based on a person's genetic makeup. A genetic predisposition results from specific genetic variations that are often inherited from a parent. These genetic changes contribute to the development of a disease, but do not directly cause it. For example, mutations in the *BRCA* gene result in an increased risk for ovarian cancer. Some people with a predisposing genetic variation will never get the disease while others will, even within the same family. Genetic variations can have large or small effects on the likelihood of developing a particular disease. Although each of these variations only slightly increases a person's risk, having changes in several different genes may combine to increase disease risk significantly. Changes in many genes, each with a small effect, may underlie susceptibility to many common diseases, including cancer.

In people with a genetic predisposition, the risk of disease can depend on multiple factors in addition to an identified genetic change. These include other genetic factors (sometimes called modifiers) as well as lifestyle and environmental factors. Diseases that are caused by a combination of factors are described as multifactorial. Most disease-causing gene mutations are uncommon in the general population. However, other genetic changes occur more frequently. Genetic alterations that occur in more than 1 percent of the population are called polymorphisms.

Acquired (or somatic) mutations occur at some time during a person's life and are present only in certain cells, not in every cell in the body. These changes can be caused by environmental factors such as ultraviolet radiation from the sun, chemical exposure, or can occur if an error is made as DNA copies itself during cell division. Acquired mutations in somatic cells (other than sperm and egg cells) cannot be passed to the next generation.

Environmental and occupational exposures to natural substances, as well as man-made chemical and physical agents, play a causative role in human cancer. Acquisition of cancer-specific alterations may be triggered by the mutational and/or non-mutational (i.e., epigenetic) events in the genome which, in turn, affect gene expression and downstream phenotypes including persistent proliferative signaling, resistance to cell death, evasion of growth suppression, replicative immortality, inflammatory response,

deregulation of energy metabolism, genomic instability, induction of angiogenesis, and activation of invasion ultimately resulting in metastases.

Genotoxic carcinogens are agents that interact directly or after metabolic activation with DNA, causing mutations and leading to tumor formation. Non-genotoxic carcinogens are a diverse group of chemical compounds that are known to cause tumors by mechanisms other than direct damage to DNA. In a broad sense, carcinogenesis may be induced through either genotoxic or non-genotoxic mechanisms. However, both genotoxic and non-genotoxic carcinogens also cause prominent epigenetic changes (Pogribny and Rusyn, 2013). Disruption of epigenetic processes can lead to altered gene function and malignant cell transformation. Global changes in the epigenetic landscape are a hallmark of cancer.

The presence of talc particles in the ovaries (deep in the tumor) of some ovarian cancer patients and presence of talc in pelvic lymph nodes provides indirect evidence for talc carcinogenicity (Heller et al., 1996). Changes in signal transduction pathways that lead to increased and chronic inflammation are also associated with cancer, as are changes in cancer stem cells which have the ability to generate tumors through the processes of self-renewal and differentiation into multiple cell types. Cancer stem cells are thought to play a major role in tumor escape, chemoresistance/recurrence of ovarian cancer. Users of talcum powder have lower plasma levels of anti-MUC1 antibodies than non-users (Karageorgi et al., 2010). MUC1 is a protein highly expressed by ovarian, breast, and endometrial tumors, and low levels of anti-MUC1 antibodies are associated with poorer prognosis. Reducing immunity to MUC-1 could be one mechanism by which talc increases endometrial and/or ovarian cancer risk (Karageorgi et al. 2010).

C. Ovarian Cancer

There are two major categories of ovarian carcinogenesis based on the idea that tumors are heterogeneous: high-grade malignancies that tend to be fast growing and chemo-sensitive, and low-grade neoplasms which typically grow slowly, but are less sensitive to chemotherapy. The low-grade pathway is associated with a stepwise mutation process, whereas the high-grade develops through genetic instability (Lengyel, 2010). Ovarian cancer comprises at least five distinct histological subtypes, the most common and well-studied being high-grade serous ovarian cancer. The majority of these tumors arise from the distal end of the fallopian tube and evolve from premalignant lesions called tubal intraepithelial carcinoma (Saad, 2010). Several risk factors have been associated with increased risk of ovarian cancer and include: low parity, infertility, early age of menarche and late age of menopause.

Multiple mechanisms can explain the progression of ovarian cancer (Fleming et al., 2006; Fathalla, 2013; Saad, 2010; Smith and Xu, 2008). These mechanisms include: incessant ovulation-whereby repeated damage and trauma to the ovarian epithelium during ovulation increases the risk for genetic mutation and ovarian neoplasm during epithelium repair; pituitary gonadotropin changes- high levels of gonadotropins increase estrogen stimulation which can cause ovarian epithelial cells to become entrapped in inclusion cysts that undergo malignant changes; androgen/progesterone alterations-androgens stimulate ovarian cancer formation and progestins are protective; inflammation- factors that predispose to inflammation, such as endometriosis, PID, perineal talc use and hyperthyroidism could stimulate ovarian cancer. The molecular pathway in the inflammatory process involves intracellular

effectors implicated in malignant transformation such as VEGF, NF-κB, nitric oxide synthase, and cyclooxygenase (Williams et al., 1999).

Genetic mutations also play a role in the development of ovarian cancer. For example, certain mutations in the *BRCA1* or *BRCA2* genes increase a person's risk of developing ovarian cancer. Both inherited and acquired gene mutations work together to cause cancer. Even if one has inherited a genetic mutation that predisposes one to cancer, that doesn't mean he or she is certain to get cancer. Rather, one or more additional gene mutations may be needed to cause cancer. The inherited gene mutation could instead make one more likely to develop cancer when exposed to certain cancer-causing substances.

D. Roles of the Immune System

It is well established that inflammation has paradoxical roles during tumor development (Coussens and Werb, 2002). While acute inflammation can be protective against tumors, chronic inflammation provides an environment for the tumor to thrive. The net outcome of tumor-associated inflammation depends on the dominance of either tumor-promoting or tumor-suppressive actions. Inflammation normally functions to maintain tissue homeostasis in response to tissue stressors such as infection or tissue damage. However, studies also suggest a close association between inflammation and tumorigenesis (Rakoff-Nahoum, 2006).

Two stages of inflammation exist, acute and chronic inflammation (Ingersoll, 2011). Acute inflammation is an initial stage of inflammation (innate immunity), which is mediated through the activation of the immune system. This type of inflammation persists only for a short time and is usually beneficial for the host. Acute inflammation (e.g., involving innate immunity, macrophages, natural killer cells, neutrophils) frequently precedes the development of protective adaptive immune responses to pathogens and cancer.

Chronic inflammation, by contrast, has been shown to contribute to tumorigenesis at all stages (Crusz and Balkwill, 2015). It contributes to cancer promotion by inducing cellular proliferation; and to cancer progression by enhancing angiogenesis and tissue invasion. Over time, chronic inflammation can cause DNA damage and lead to cancer. Inflammation initiated by genital application of talc is likely to be sustained, since studies indicate that women start using talcum powder at an early age and continue using it for decades.

E. Ovarian Cancer and Inflammation

Inflammation plays an important role in the progression of ovarian cancer, and it is a biologically plausible mechanism that mediates ovarian cancer. Recent clinical and prospective data suggest that C-reactive protein (CRP), a marker of global inflammation, is associated with increased ovarian cancer risk (Li, 2017; Poole, 2013; Jing, 2017). Other inflammatory markers may be important in ovarian carcinogenesis. In premenopausal women, ovarian epithelial cells secrete cytokines as part of ovarian function and some of these cytokines are also produced by ovarian cancer cells (Jammal, 2016). Epithelial

cells in proximity to ovulating follicles are likely exposed to these inflammatory mediators that may signal oxidative stress, and enhance the risk of mutagenesis. Importantly, cytokines involved in ovarian function, follicle rupture, and repair (physiologic processes before menopause) are suggested to remain activated in postmenopausal women and may play an etiologic role in ovarian carcinogenesis; these cytokines include: interleukin (IL)-1α, IL-1β, IL-2, IL-6, IL-8, IL-10, tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), granulocyte colony- stimulating factor (G-CSF), and granulocyte macrophage colony-stimulating factor (GMCSF). Many inflammatory mediators, including prostaglandins, leukotrienes, and cytokines, are locally elevated during ovulation. Epithelial cells in proximity to ovulating follicles are likely exposed to these inflammatory mediators that may signal oxidative stress, and enhance the risk of mutagenesis. Moreover, IL-8, an important angiogenesis factor, is elevated in ovarian cancer patients and is believed to be a key factor for cancer growth and new vessel formation (Lane, 2011). Additionally, Saed et al. (2017) has reported that oxidative stress can play an important role in the pathogeneis, neoangiogenesis and dissemination of local or distant ovarian cancer.

Endometriosis is a pelvic disorder associated with inflammation and scarring. Studies also link endometriosis with the increased risk of epithelial ovarian carcinoma through pathways related to oxidative stress and inflammation (Melin, 2006; Worley, 2013). Studies indicate that women with endometriosis differ in the expression of inflammatory mediators, and changes in the cytokine network indicating immune dysregulation, which could contribut to the development of endometriosis (Pizzo, 2002). Wu et al. (2009) performed a study to determine the role of talc in the development of ovarian cancer, considering the history of endometriosis. Results demonstrated an increased risk of ovarian cancer with increasing frequency and duration of talc use; compared to never users, risk was highest among long duration, frequent talc users. A history of physician-diagnosed endometriosis was significantly associated with ovarian cancer in risks, and women who were talc users and had a history of endometriosis showed a 3-fold increased risk, and authors concluded risk of ovarian cancer is significantly associated with talc use and a history of endometriosis.

VIII. MECHANISM OF INFLAMMATION

Inflammation has long been associated with the development of cancer (reviewed by Heidland, 2006; Balkwill, Mantovani, 2001; Rakoff-Nahoum, 2006; Todoric, 2016). An inflammatory process begins when chemical mediators are released by the damaged tissue. The inflammatory response orchestrates host defenses and mediates tissue repair and regeneration in response to damage from chemical toxicants, foreign organisms or carcinogens. Epidemiological evidence points to a connection between inflammation and a predisposition for the development of cancer, i.e., long-term inflammation leads to the development of dysplasia (abnormal cell growth preceding cancer).

Inflammation is a well-established risk factor for all stages of carcinogenesis and tumor progression (Chow, 2012), including ovarian cancer (Maccio and Madeddu, 2012). Inflammation is a factor in a number of mechanisms regarding the etiology of epithelial ovarian cancer and a contributor to

ovarian tumor development and tumor progression (reviewed in Ness, 1999). Inhibition of inflammatory cytokines in the tumor milieu acts on inflammatory-induced angiogenesis and apoptosis and improves prognosis. In a review paper by Ness and Cottreau (1999), talc and asbestos are discussed as risk factors for ovarian cancer, along with endometriosis and pelvic inflammatory disease which are all associated with induction of local cancer.

A. Cytokine Networks

The cytokine networks are very active in producing pro-inflammatory cytokines, growth factors, and chemokines, all of which are molecules active in immune system signalling. There is evidence that inflammatory cytokines and chemokines, which are produced by tumor cells and/or tumor-associated leukocytes, may contribute directly to malignancy. Tumor necrosis factor (TNF)-alpha, a major mediator of inflammation, has actions directed towards both tissue destruction and recovery. TNF can be detected in malignant and/or stromal cells in human ovarian, breast, prostrate, bladder and colorectal cancer, lymphomas and leukemias and often is associated with IL- 1 and -6 and macrophage colony stimulating factor. TNF-α is also implicated in the induction of a chemokine called MCP-1 which can regulate the macrophage and lymphocyte infiltrate and of MMP-9 in the ovarian tumor microenvironment. There is also evidence for pro-cancer actions of TNF-α in animal models. The molecular basis is thought to involve induction of ROS in the form of NO synthase. NO can directly oxidize DNA, resulting in mutagenic changes, and may damage some DNA repair proteins. Inducible NO synthase has been detected in gynegological cancers, including ovarian cancer.

B. Macrophages

The neoplastic process which consists of proliferation, survival and migration is linked with the tumor microenvironment and synchronized with the influx of inflammatory cells, including neutrophils and macrophages which are a main source of exogenous reactive oxygen species (ROS) (Forman and Torres, 2002). Macrophages and the innate immune system can be responsible for tissue injury, when in excess or continuous.

This can also indicate macrophage activation leading to excess production of other macrophage-generated mediators, including cytokines. Macrophages can engulf talc particles and play a critical role in disease. Moreover, macrophages are the major constituents in granulomas. Talc can promote murine macrophage survival and DNA synthesis *in vitro* (Hamilton, 2001). Such enhancement of macrophage survival by talc, if it occurred *in vivo*, could lengthen the cells' tenure in a lesion with the result that more cells would be present to produce inflammatory mediators, such as cytokines, proteinases, and eicosanoids, perhaps potentiated by additional stimuli. This could be another mechanism as to how macrophage cell numbers increase in talc-induced granulomas and inflammatory reactions.

In a 2005 *in vitro* study (Bogatu and Contag, 2005), talc (as a fibrogenic dust) was shown to adsorb high density lipoprotein (HDL). The authors concluded that the adsorption of HDL could have a "causal relationship" with triggering of a fibrotic reaction. The adsorption on the surface of fibrogenic dust particles, including talc provides an opportunity for the intake of HDL by macrophages which then

release an increased amount of fibrogenic mediators. Coating of talc by HDL allows for more rapid uptake by the macrophage as it can use multiple receptors as points of entry into the cell. In general, surfaces of all fibrogenic particles, such as talc, have a specific property which is lacking in non-fibogenic (inert) particles or is at least significantly less effective. However, even upon overloading, non-fibrogenic dusts cannot produce fibrosis.

In another study (Ghio et al., 2012), both mesothelial and airway epithelial cells exposed to talc significantly increased iron importation and concentration of the iron storage protein, ferritin. The production of pro-inflammatory cytokines was also induced by *in vitro* talc exposure relative to control lung tissue, and a time-dependent and concentration-dependent release of oxidents was observed in both cell types. Talc toxicity was also observed in an *in vitro* study comparing effects of micro-scale talc particles with those of smaller nanotalc particles on lung cells (Akhtar, 2010). Cell viability was decreased for all talc exposures, and decreased as a function of talc concentration, origin and particle size. Nanotalc particles differentially induced lipid peroxidation, reactive oxygen species and depletion of the anti-oxidant, glutathione. Further, data suggests that talc toxicity was mediated through oxidative stress.

A study by Khan et al. (2011) demonstrated that nanoscale talc, as opposed to larger talc particles enhanced its cytotoxicity. In this study, macrophages exposed to nanotalc increased the manufacture (transcription) of three macrophage-released pro-inflammatory cytokines and the phosphorylation of two signal transduction pathways. The authors indicated that the inflammatory potential of nano talc particles might be (at least partially) a potential mechanism in talc-mediated pathogenicity.

An early study (Davies et al., 1983) in which the cytotoxicity of seven talcs was evaluated using rat peritoneal macrophage demonstrated modest, but consistent macrophage cytotoxicity visualzed by an increase in macrophage production of two enzymatic cell injury markers including lactate dehydrogenase (LDH) and B-glucuronidase (compared to *in vitro* treatment with a non-fibrogenic dust. This study points to the potential of talc to “activate” macrophage leading to increased production of macrophage-released mediators including pro-inflammatory cytokines. Some investigators have suggested such *in vitro* macrophage changes could predict fibrogenicity *in vivo*. Based on talc chemical analyses, the authors concluded that effects on macrophages were not due to contaminating minerals.

In a molecular cell study by Shukla et al. (2009), non-fibrous-containing talc at low concentrations caused increased expression of the gene Activating Transcription Factor (ATF genes modulates production of pro-inflammatory cytokines and growth factors in human lung cells) in cultured mesothelial cells at 8 hr and no changes at 24 hr, whereas expression levels of 30 genes were elevated at 8 hr at high talc concentrations.

Tumor necrosis factor (TNF)-α is a cell signaling protein produced by macrophages, primarily involved in the regulation of immune cells. Pre-diagnostic serum levels of 46-inflammation –related biomarkers were measured in 149 incident ovarian cancer cases and matched controls. As his been discussed in several aforementioned sections of this Report, C-reactive protein (CRP), IL-1-α and TNF-α proved to all be significantly elevated and associated with increased cancer risk. In analyses restricted to serous ovarian cancer (n=83), the associations with CRP and IL-8 remained or strengthened. Thus, IL-8

can also be considered an inflammatory biomarker of ovarian cancer (Trabert et al., 2014), again demonstrating talc's action as an inflammatory agent. Iron and its homeostasis are intimately tied to the inflammatory response (Wessling-Resnik, 2010). Talc has been shown to modulate TNF- α and IL-6 production by its binding to iron (Ghio, 2011). TNF-α, like CRP, is a marker of various inflammation processes. TNF-α has been shown to play a role in later steps of carcinogenesis. For example, NF-κB activation by TNF- α is involved in neoplastic transformation, proliferation, and tumor survival. In addition, in ovarian cancer cells, TNF-α enhances cell migration and metastasis through the action of NF-κB. TNF-α was positively associated with ovarian cancer in case-control studies using serum samples collected at diagnosis.

C. Role of Oxidants in Ovarian Cancer

The chronic inflammatory states associated with infection and irritation may lead to environments that foster genomic lesions and tumor initiation. One effector mechanism by which the host system responds to insult is production of free radicals such as reactive oxygen species (ROS), hydroxyl radical (OH•) and superoxide (O_2-•) and reactive nitrogen species (RNS), nitric oxide (NO•) and peroxynitrite (ONOO). Primarily thought to be anti-microbial, these molecules form due to the activities of host enzymes such as myeloperoxidase, NADPH oxidase, and nitric oxide, which are regulated by inflammatory signaling pathways. Importantly, ROS and RNS lead to oxidative damage and nitration of DNA bases which increase the risk of DNA mutations.

During inflammation, macrophages, mast cells and neutrophils are recruited to the site of damage, which leads to a 'respiratory burst' due to an increased uptake of oxygen, and thus, an increased release and accumulation of ROS at the site of damage. A sustained inflammatory/oxidative environment leads to a vicious circle, which can damage healthy neighboring epithelial and stromal cells and over a long period of time may lead to carcinogenesis. Oxidative stress can also activate a variety of transcription factors. Activation of these transcription factors can lead to the expression of over 500 different genes, including those for growth factors, inflammatory cytokines, chemokines, cell cycle regulatory molecules, and anti-inflammatory molecules that can also be linked to cancer. Under a sustained environmental stress, ROS are produced over a long time, and thus significant damage may occur to cell structure and functions that could induce neoplastic transformation. In general, the longer the inflammation persists, the higher the risk of cancer.

Following an inflammatory stimulus, initiation of carcinogenesis mediated by ROS may be direct (oxidation, nitration, halogenation of nuclear DNA, RNA, and lipids), or mediated by the signaling pathways activated by ROS (Reuter, 2010; Saed, 2011; Saed, 2017). Hydrogen peroxide plays an important role in carcinogenesis because it is capable of diffusing through cell membranes and producing many types of cell injury. NO is another free radical implicated in carcinogenesis (Saed, 2017). iNOS, calcium-independent isoform, produces large amounts of NO and is only expressed during inflammation. ROS can specifically activate certain signaling pathways and thus contribute to tumor development through the regulation of cellular proliferation, angiogenesis, and metastasis.

1. Talc-Induced Inflammation and Oxidative Stress

Even a single dose of a carcinogen can produce effects that are adverse to cells and tissue at the site of exposure. *In vitro* studies provide a safe and effective vehicle by which to measure those effects in a controlled environment.

Carcinogenic potential of any compound can be determined by performing a well-established methodology called a neoplastic cell transformation assay. In a 2007 study by Buz'Zard, two human ovarian cell culture lines were treated in vitro with talc from 24 to 120 hr (Buz'Zard, 2007). Another group of talc-treated cells were also treated with a specific anti-inflammatory inhibitor to determine whether talc produced transformation through the production of inflammation. Following talc treatment of both ovarian cell types, the cells' ability to grow in suspension, a key characteristic of neoplastically transformed cells, was measured - non-neoplastically-transformed normal cells cannot grow in suspension. Results showed that treatment with talc can transform ovarian cells which further demonstrates the carcinogenic potential of talc. As anti-inflammatory treatment reduced formation of ROS and number of transformed colonies, a relationship between cell transformation and inflammation was demonstrated. Interestingly, exposure of ovarian cells to talc also increased ROS generation in this study in a time and dose-dependent manner. These effects could be linked with neoplastic changes as chronic inflammation is associated with cancer induction and ROS are often seen as a component of the tumor microenvironment. Human neutrophils exposed to talc in this study also increased ROS generation significantly compared to control phagocytes.

In a study carried out by Keskin in 2009, rats exposed to talc produced an increase in ovarian follicles which could be related to the " ovulation theory" associated with ovarian cancer, thus demonstrating a plausible mechanism for talcum powder-induced ovarian cancer.

Recent data demonstrates the importance of oxidative stress in ovarian cancer. The effects of talcum powder exposure on oxidative stress levels in normal ovarian epithelial cells, ovarian epithelial cells and cancerous ovarian epithelial cells were measured (Saed, 2017; Fletcher, 2018 (abstract)). Studies indicate that epithelial ovarian cancer manifests a persistent pro-oxidant state through alteration of the redox balance by the up-regulation of several oxidant enzymes in epithelial ovarian caner tissues (Saed, 2018). Advancing similar work, in a recently accepted abstract, Harper and Saed report a mechanism by which talc enhances the pro-oxidant state in normal (ovarian and tubal) and ovarian cancer cells, through induction of gene point mutations (corresponding to known specific single nucleotide polymorphisms - SNPs) in key oxidant enzymes, altering their activities (Harper and Saed, 2018).

Emerging science by Fletcher (2018) demonstrated that talc-treated ovarian cancer cell lines and normal ovarian epithelial cells showed a marked increase in mRNA levels of pro-oxidant enzymes, including iNOS and MPO. This shift to a pro-oxidant environment indicates oxidative stress as early as 24 hours after exposure. These recent facts provide strong support for the ability of talc to produce an oxidant state that leads to inflammation and in turn epithelial ovarian cancer. This latter study shows that talcum powder enhances the redox state as part of the inflammatory cascade in both normal ovarian

epithelial cells and in ovarian cancer cells, revealing a plausible mechanistic underpinning for talc-induced ovarian cancer.

Another study by the same authors showed that talcum powder exposure increased levels of the cancer antigen, CA-125, in both normal ovarian cells and ovarian cancer cells. (Fletcher and Saed, 2018). CA-125 is an antigen that is elevated in some patients with specific types of cancers, and is used as a biomarker for ovarian cancer detection, providing further information about talcum powder's carcinogenic properties.

In a study by Shim et al. (2015), inhalation of talc revealed infiltration of macrophages and the increased expression of the antioxidant, superoxide dismutase indicating oxidative stress in rats. Moreover, in the same study inhalation of talc demonstrated macrophage aggregations and oxidative damage in the lungs. Intrapleural injection of talc particles produced an acute serum inflammatory response, more pronounced with smaller particles (Genofre et al., 2009). In addition, talc exposure induced vasoconstriction in the brain via the action of superoxide anions (Mori et al., 1995). Non-fibrous talc at low *in vitro* exposure concentrations caused increased expression of transcription factors associated with the inflammatory process in a time and dose-dependent manner (Shukla et al., 2009). Nano-talc exposure enhanced the production of pro-inflammatory cytokines by macrophages *in vitro* (Khan et al., 2011). Also, pre-treatment of macrophage (prior to talc exposure) with inflammatory signal transduction inhibitors reduced TNF mRNA stability demonstrating their role in TNF mRNA stabilization and expression (Khan et al., 2011).

In an epidemiological study, talc exposure was significantly associated with ovarian cancer in women who lacked a specific anti-oxidant genotype (glutathione-S transferase M1/T1) (Gates et al., 2008). Finally, talc exposure increases COX2, an enzyme that plays a critical role in inflammation (Pace et al., 2006).

At high concentrations or chronic exposure, ROS can damage cellular macromolecules and contribute to neoplastic transformation and/or tumor growth. Other likely manifestations of talc-induced inflammation include reduced fibrinolysis, activation of neutrophils and macrophages and increased production of cytokines and growth factors, and these have been suggested to occur in the peritoneum in response to contamination by surgical glove powder (Merritt et al., 2008).

In sum, inflammation is a primary mediator of ovarian cancer. As the scientific studies outlined above demonstrate, talcum powder products cause inflammation that can result in an elevation of biomarkers; changes in cell signaling; activation of chemokines and cytokines; changes in the oxidative environment; gene alterations and/or mutations; inhibition of apoptosis and induces neoplastic transformation and prolifearation (i.e., cancer). This talcum powder-induced inflammatory cascade provides significant biologic and toxicologic support for a conclusion that talcum powder products can cause ovarian cancer.

D. Iron-Facilitated Inflammation

Talc particles can bind iron and iron facilitates inflammation and ROS production; surfaces of silicates including talc has a net negative charge on the surface which generates a capacity for the adsorption and exchange of cations like iron which has a high affinity for oxygen-donor ligands. According to J&J documents from Luzenac America Technical Center, heavy metal analyses on Grade 66 Non-Shear Disk Test Run samples demonstrated very high levels of iron (15,200 – 21,500 mg/kg) that could cause oxidative stress and an inflammatory response. Multiple studies have demonstrated that exposure to talc disrupts iron homeostasis, oxidative stress, and causes a fibro-inflammatory response (Akhtar et al., 2010; Ghio et al., 1992; Ghio et al., 2012). Talc exposure significantly increases iron importation and concentrations of ferritin (iron storage protein). The accumulation of iron, the accompanying oxidative stress, and inflammatory events after exposure to talc are comparable to those with other forms of particulate matter. The capacity of talc particles to support the *in vitro* generation of oxidants in an acellular environment was significantly affected by the concentration of associated iron, with talc-Fe producing a significantly greater signal for lipid peroxidation relative to talc alone (Akhtar, 2010). This relationship is supported by inhibition of the effect by addition of a metal chelator and a hydroxyl radical scavenger. The disruption of cell iron homeostasis is frequently associated with oxidative stress and inflammation.

IX. SUMMARY OF OPINIONS

I hold the following opinions to a reasonable degree of scientific certainty:

1. Based on the scientific literature and the testing results that I have seen by Defendants and Drs. Longo and Rigler, it is my opinion that talcum powder products, including Johnson's Baby Powder and Shower to Shower, may contain known carcinogens, including asbestos, fibrous talc, and heavy metals. In addition, these products contain fragrance chemicals, many of which are inflammatory agents, toxicants, or potential carcinogens.

2. Talcum powder can reach the ovaries through two routes with anticipated use: 1) perineal application (dermal) with migration/transport through the genital tract via the vagina, uterous, and fallopian tubes; and, 2) inhalation of talcum powder particles. Through either route, talcum powder and its constituents could reach the lymphatic system and bloodstream.

3. Exposure to talcum powder products causes an inflammatory tissue reaction which may result in the following:
    a. Elevation of increased inflammatory markers;
    b. Changes in cell signaling;
    c. Activation and/or release of chemokines and cytokines;
    d. Changes in the oxidative environment;
    e. Gene alterations and/or mutations;
    f. Inhibition of apoptosis; and

g. Neoplastic transformation and proliferation

4. Based on knowledge of the carcinogenic components of talcum powder products, the potential of the powder, with its components, to reach the ovaries and the resultant inflammatory tissue response, it is biologically plausible for talcum powder products to cause ovarian cancer.

I reserve the right to amend or modify this report as new information becomes available. I have not testified in litigation over the previous 4 years. I am charging $ 350 per hour for my work on this matter.

Exhibit A

JUDITH TERRY ZELIKOFF, Ph.D.
Tenured Professor

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EDUCATION

1973: Bachelor of Science (**Biology**)
Upsala College
East Orange, NJ

1976: Master of Science **(Microbiology)**
Farleigh Dickinson University
Department of Biology
Teaneck, NJ,
in conjunction with,
UMDNJ-New Jersey Medical School
Department of Neuroscience
Newark, NJ
Thesis Dissertation: Herpes Simplex Virus-IgM Specific Antibodies in Guillian-Barre Syndrome

1982: Doctor of Philosophy (**Experimental Pathology**)
UMDNJ-New Jersey Medical School
Department of Pathology
Newark, NJ
Thesis Dissertation: Cytoskeletal Modifications of Human Fibroblasts that Occur During a Complement-Dependent Cytotoxic Antibody Response

PROFESSIONAL EXPERIENCE

1982-Present: ***NEW YORK UNIVERSITY SCHOOL OF MEDICINE***
Institute of Environmental Medicine
Tuxedo, NY

2005- Present: Tenured Professor
Laboratory of Pulmonary & Systemic Toxicology

Developmental Immunotoxicology: Effects of fetal insults on later life immune-related diseases in the offspring.

Pulmonary Immunotoxicology: Characterization of inhaled metal, gaseous, and airborne pollutant mixtures including woodsmoke and tobacco smoke, on pulmonary immune defense mechanisms and host resistance against infectious disease and asthma.

Environmental Toxicology/Ecoimmunotoxicology: Effects of aquatic pollutants on the immune responses of fish; development of immune biomarkers. Alternate animal models for immunotoxicological studies.

1995-2005: Associate Professor (Tenured in 1997)
Laboratory of Systemic Toxicology

1989-1995: Assistant Professor
1986-1989: Research Assistant Professor
Laboratory of Pulmonary Biology
Laboratory of Environmental Toxicology

Environmental Toxicology: Characterization of aquatic pollutants and immune defense mechanisms of fish. Studies concerning drug bioaccumulation and metabolism in different fish species.

Inhalation/Pulmonary Toxicology: Effects of ambient pollutants on macrophage metabolism and immune function.

1984-1986: Associate Research Scientist
Laboratory of Environmental Toxicology

Genetic Toxicology: Clastogenic/mutagenic effects of complex environmental mixtures.

Cell Biology: Establishment of primary cultures for assessing the toxicity of environmental contaminants *in vitro*.

1982-1984: NIH (NHLBI) Post-Doctoral Fellow
Laboratory of Environmental Toxicology

Genetic Toxicology: Development of short-term *in vitro* bioassays to detect carcinogens, promoters and co-carcinogens in complex environmental mixtures.

1977-1978: *PFIZER PHARMACEUTICAL*
Laboratory of Chemical Carcinogenesis
Maywood, NJ

Assistant Research Scientist
Laboratory studies using animal models and *in vitro* mammalian cell systems to investigate chemical- and viral-induced carcinogenesis.

1974-1975: *VA HOSPITAL /UMDNJ-NEW JERSEY MEDICAL SCHOOL*
Department of Neuroimmunology
East Orange, NJ

Associate Research Scientist
Laboratory studies investigating the etiology of viral-induced neuropathologies

TEACHING EXPERIENCE - NATIONAL

1990-Present: *NEW YORK UNIVERSITY SCHOOL OF MEDICINE*
Department of Environmental Medicine
Tuxedo, NY
Graduate Courses

- Global toxicology & community health (NYU Global College of Public Health: Organizer/Director, Fall, 2018; offered every year)
- Environmental Immunotoxicology (Organizer/Director, 1993-present)
- Organ System Toxicology (Director, 2001-present)
- Toxicology (Biology-cross linked: Director, 2010 – present)
- Communication Skills (Lecturer; 2010-present)
- Principles of Toxicology (Lecturer; 1992-present)
- Environmental Physiology of the Respiratory Tract (Lecturer; 1992– 1994)

1979-1994: *WILLIAM PATERSON COLLEGE*
Department of Biology
Wayne, NJ

Adjunct Professor
Undergraduate Courses

- Microbiology lecture and laboratory (1979 - 1984)
- Human biology lecture and laboratory (1979 - 1994)

1991-1994: *ROCKLAND COMMUNITY COLLEGE*
Department of Biology
Suffern, NY

Adjunct Professor
Undergraduate Courses

- Microbiology lecture and laboratory

1979-1982: *SETON HALL UNIVERSITY*
Department of Biology
South Orange, NJ

Research Scientist/Graduate Assistant
-Laboratory studies in immunopathology, virology, viral immunology, and microbiology

-**Undergraduate and Graduate Courses**

- Bacteriology lecture and laboratory
- Advanced Microbiology
- Cell biology/Virology techniques

1976-1979: *FAIRLEIGH DICKINSON UNIVERSITY*
Department of Biology
Teaneck, NJ

Adjunct Professor
Undergraduate and Graduate Courses

- General biology lecture and laboratory

- o Human genetics
- o Immunology

TEACHING EXPERIENCE - INTERNATIONAL

2013-present *UNIVERSITY OF PORT HARCOURT (Port Harcourt, Nigeria)*
Dept. of Toxicology
Lecturer in graduate toxicology course

2002-present: *CHULABHORN RESEARCH & GRADUATE INSTITUTE (Professor, Course Director)*
Department of Toxicology
Bangkok, Thailand
Graduate Course (3 weeks- given every even year)
- o Environmental Immunotoxicology and Reprotoxicology

1999 **1999-2000:** *UNIVERSITY OF TASMANIA (Adjunct Professor)*
Department of Environmental Toxicology
Tasmania, Australia
Graduate Course (2 weeks)
- o Fish Immunology & Immunotoxicology (Organizer/Director; Lecture and Lab)

1999-2000: *LINCOLN UNIVERSITY*
Department of Environmental Health Sciences
Christ Church, New Zealand
Graduate Course (2 weeks)
- o Fish Immunology & Immunotoxicology (Organizer/Director; Lecture and Lab)

HONORS AND AWARDS

- 2018 – Society of Toxicology (SOT), Education Award
- 2015 – SOT, Women in Toxicology Mentorship Award
- 2013 – West African SOT (WASOT), Distinguished Recognition
- 2012 - 2014, SOT, Distinguished Service as SOT Secretary
- 2012 - SOT, Global Senior Scholar Host Award
- 2012 – SOT, Career Achievement Award in Immunotoxicology
- 2008 – Mid-Atlantic Chapter Society of Toxicology, President

PUBLICATIONS

Peer-reviewed Journals (In ascending order)

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2. **Zelikoff, J.T**., J.M. Daisey, K. Traul and T.J. Kneip. Balb/c 3T3 cell transformation response to organic extracts of airborne particulate matter as seen by their survival in aggregate form. *Mutat. Res.* 144: 107-116 (1985).

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9. Schlesinger, R.B., A.F. Gunnison and **J.T. Zelikoff.** Modulation of pulmonary eicosanoid biosynthesis following exposure to sulfuric acid. *Fundam. Appl. Toxicol.* 15: 151-162 (1990).

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11. Schlesinger, R.B., L.C. Chen and **J.T. Zelikoff.** Comparative potency of inhaled acidic sulfate aerosols: The influence of specific components and the role of H^+ ions. *Environ. Res.* 52: 210-224 (1990).

12. Schlesinger, R.B., P.A. Weideman and **J.T. Zelikoff.** Effects of repeated exposure to ozone on respiratory tract prostanoids. *Inhal. Toxicol.* 3: 27-36 (1991).

13. **Zelikoff, J.T.**, N.A. Enane, D. Bowser, K.S. Squibb and K. Frenkel. Development of fish peritoneal macrophages as a model for higher vertebrates in immunotoxicological studies. I. Characterization of trout macrophage morphological, functional and biochemical properties. *Fundam. Appl. Toxicol.* 16: 576-589 (1991).

14. **Zelikoff, J.T**., G.L. Kreamer, M.C. Vogel and R.B. Schlesinger. Immunomodulating effects of ozone on macrophage functions important for tumor surveillance and host defense of the lung. *J. Toxicol. Environ. Health* 34: 449-467 (1991).

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103. Yao Y., Chen T., Shen SS., Niu Y., DesMarais TL., Saunders E., Fan Z., Lioy P., KluzT., Chen LC., Wu Z., Costa M., **Zelikoff J.** Malignant human cell transformation of Marcellus Shale gas drilling for flow back water. *Toxicol. Appl. Pharmacol*. 1;296:85. (2015)

104. Lauterstein, De., Tijerina PB., Corbett K., Oksuz A., Shen SS., Gordon T., Klein C., **Zelikoff JT.** Frontal cortex transcriptome analysis of mice exposed to electronic cigarettes during early life stages. *Int. J. Envron. Res. Public Health*. (2016) pii: E417. doi: 10.3390/ijerph13040417.
PMID: 27077873.

105. Gany F., Bari S., Prasad L., Leng J., Lee T., Thurston G.D., Gordon T., Acharya S., Rexford B., **J.T. Zelikoff**. Perception and reality of particulate matter (PM) exposure on New York City taxi drivers. J. Expos. Sci. Environ. Epidemiol. (In press, 2016, *Epub ahead of print; doi: 10.1038/jes.2016.23.).*

106. Kumar S., Smith-Norowitz TA., Kohlhoff S., Apfalter P., Roblin P., Kutlin A., Harkema J., Ng SP., Doherty-Lyons S., **Zelikoff JT (co-corresponding author),** Hammerschlag MR*. Exposure to cigarette smoke and *Chlamydia penumoniae* infection in mide: Effect on infectious burden, systemic dissemination and cytokine responses: A pilot study. *J. Immunotoxicol*. 13(1):77-83 (2016).

107. Iain P., Sexton K., Prytherch Z., Blum J., **Zelikoff J.T*.** (co-corresponding author), BeruBe K.A*., An *in vitro* versus in vivo toxicogenomics investigation of pre-natal exposures to tobacco smoke. Appl. *In Vitro Toxicol.* (In press, 2017).

108. Blum J.L., Chen L-C., **Zelikoff J.T*** (corresponding author). Exposure to ambient particulate matter during specific gestational periods produces adverse obstetric consequences in mice. Environ. Health Perspect. *Environ Health Perspect*; DOI:10.1289/EHP1029.

109. Gany F., Mukherjea A., Surani Z., Modayll M., Aghi M., Ulpe R., **Zelikoff J.,** Leng J., Parascandola M., Gupta P., South Asian alternative tobacco products: culture, epidemiology and policy. *J. Immigrant Minority Health*. (Jan. 2017).

110. Klocke C., Allen JL., Sobolewski M., Mayer-Proschel M., Blum JL., Lauterstein D., Zelikoff JT., Cory-Slechta. Neuropathological consequences of gestational exposure to concentrated ambient fine and ultrafine particles in the mouse. *Toxicol. Sci. Apr 1:556(2):492-508.(2017)*

111. Zelikoff, Judith T., Parmalee N., Corbett K., Gordon T., Klein C B., Aschner m. Microglia Activation and Gene Expression Alteration of Neurotrophins in the Hippocampus Following Early Life Exposure to E-cigarette Aerosols in a Murine Model. Toxicol Sci. 2017 Nov 17. doi: 10.1093/toxsci/kfx257. [Epub ahead of print]

112. Church JS, Tijerina PB, Emerson FJ, Coburn MA, Blum, JL, Zelikoff JT, Schwartzer JJ. *Perinatal exposure to concentrated ambient particulates results in autism-like behavioral deficits in adult mice. Neurotoxicology.* Nov 13. pii: S0161-813X(17)30211-5. doi: 10.1016/j.neuro.2017.10.007. [Epub ahead of print].

113. Duffy-Whritenour, J.E., S. Kennedy, and **J.T. Zelikoff**. Involvement of the neuroimmune axis in noncoplanar polychlorinated biphenyl-induced immunotoxicity. (In preparation). (*J. Immunotoxicol)*.

114. Blum, J.L., Doherty-Lyon, D., Hoffman, C., Conklin, D., Young, D. and **J.T. Zelikoff**. High fat diet exacerbates the dyslipidemic effects of prenatal exposure to cadmium nanoparticles in the adult offspring. In preparation. (*Toxicol. Sci.).*

Commentaries/Letters to the Editor/Profiles:

1. **Zelikoff, J.T.**, S. Garte and S. Belman. Response to publication "Differential phosphorylation events associated with phorbol ester effects on acceleration versus inhibition of cell growth." *Cancer Res.* 47: 389-390 (1987).
2. **Zelikoff, J.T**. Commentary on "Ecotoxicity Testing." *Toxicology and Ecotoxicology News* 1: 123-124 (1995).
3. Penn, A. and **J.T. Zelikoff.** "Profile of the Department of Environmental Medicine, New York University Medical Center." *Toxicology and Ecotoxicology News* 3: 114:116 (1996).
4. Bayne, C. and **J.T. Zelikoff,.** Meeting review on "Modulators of Immune Responses-A PhylogeneticeApproach." *Immunology Today* 20: 12-18 (1996).
5. **Zelikoff, J.T**. "Fish immunotoxicology: A new scientific discipline". *Toxicology and Ecotoxicology News*. 5: 130-132 (1996).

Book Chapters & Reports (1988 – Present,** in ascending order**):

1. Rossman, T.G., **J.T. Zelikoff**, S. Agarwal and T.J. Kneip. 1988. Genetic toxicology of metal compounds: An examination of appropriate cellular models. In: *Carcinogenic and Mutagenic Metal Compounds* 2. (E. Merian, et al., Eds), Gordon and Breach Science Publishers, NY. pp. 195-206.
2. **Zelikoff, J.T.** and Enane, N. 1991. Assays used to assess the activation state of rainbow trout peritoneal macrophages. In: *Techniques in Fish Immunology-2* (J.S. Stolen, et al., Eds.), SOS Publications, NJ. pp. 107-124.
3. **Zelikoff, J.T**. 1993. Immunological alterations as indicators of environmental metal exposure. In: *Modulators of Fish Immune Response: Models for Environmental Toxicology/Biomarkers, Immunostimulators*-Vol. 1 (J.S. Stolen, T. Fletcher, **J.T. Zelikoff**, S.L. Kaattari, D.P. Anderson, and L.E. Twerdok, Eds.), SOS Publications, NJ. pp. 101-110.

4. **Zelikoff, J.T**. and D. Bowser. 1994. Care and short-term laboratory maintenance of rainbow trout in laboratories with limited aquatic facilities. In: *Techniques in Fish Immunology*-3 (J.S. Stolen, et al. Eds.), SOS Publications, NJ. pp. 13-14.
5. **Zelikoff, J.T.** 1994. Fish immunotoxicology. In: *Immunotoxicology and Immunopharmacology* (J. Dean, M. Luster, A. Munson, I. Kimber Eds), Raven Press, NY. pp. 386-403.
6. **Zelikoff, J. T**. and M. D. Cohen 1995. Immunotoxicity of inorganic metal compounds. In: *Immunotoxicology.* (R. Smialowicz, and M. Holsapple, Eds.), CRC Press, Boca Raton, FL. pp. 125-146.
7. **Zelikoff, J.T.**, W. Wang, N. Islam, L.E., Twerdok, M. Curry, J. Beaman, and E. Flescher. 1996. Assays of reactive oxygen intermediates and antioxidant enzymes in medaka *(Oryzias latipes*): Potential biomarkers for predicting the effects of environmental pollution. In: *Techniques in Aquatic Toxicology*. (G. Ostrander Ed.), CRC Press, FL. pp. 178-206.
8. **Zelikoff, J.T.** W. Wang, N. Islam, E. Flescher, and L.E. Twerdok. 1996. Heavy metal-induced changes in antioxidant enzymes and oxyradical production by fish phagocytes: Application as biomarkers for predicting the immunotoxic effects of metal-polluted aquatic environments. In: *Modulators of Immune Responses-A Phylogenetic Approach* - Vol. 2 (J. Stolen, **J.T. Zelikoff**, L.E. Twerdok, D. Anderson, C. Bayne, C. Secombes, T. Fletcher, Eds.), SOS Publications, NJ. pp. 135-148.
9. Twerdok, L.E., J.R. Beaman, M.W. Curry, and **J.T. Zelikoff**. 1996. Health status determination and monitoring in an aquatic model *(Oryzias latipes*) used in immunotoxicological testing. In: *Modulators of Immune Responses - A Phylogenetic Approach*-Vol. 2 (J. Stolen, **J.T. Zelikoff**, L.E. Twerdok, D. Anderson, C. Bayne, C. Secombes, T. Fletcher, Eds.), SOS Publications, NJ. pp. 210-215.
10. Benson, J. and **J.T. Zelikoff**. 1996. Respiratory toxicology of metals. In: *Toxicology of Metals*. (L.W. Chang, Ed.), CRC Press, FL. pp. 929-938.
11. **Zelikoff, J.T**. and R. 1996. Smialowicz. Metal-induced alterations in innate immunity. In: *Toxicology of Metals.* (L.W. Chang, Ed.), CRC Press, FL. pp. 811-826.
12. **Zelikoff, J.T**., W. Wang, N. Islam and L.E. Twerdok. 1997. Immune responses of fish as biomarkers to predict the health effects of aquatic pollution: Application of laboratory assays for field studies. In: *Ecotoxicology: Responses, Biomarkers and Risk Assessment* (J.T. Zelikoff, J. Schepers, J. Lynch, Eds.), SOS Publications, Fair Haven, NJ. pp. 218-235.
13. **Zelikoff, J.T.** and M.D. Cohen. 1997. Metal Immunotoxicology. In: *Handbook of Human Toxicology*, (E.J. Massaro, Ed.), CRC Press, Boca Raton, FL. pp. 811-852.
14. Thomas, P.T. and **J.T. Zelikoff.** 1999. Air pollutants: Modulators of pulmonary host resistance against infection. In: *Air Pollutants and Effects on Health*. (S.L. Hogate, H.S. Koren, J.M. Samet, R.L. Maynard, Eds.), Academic Press, London. pp. 420-450.
15. **Zelikoff, J.T**., C. Nadziejko, K. Fang, T. Gordon, C. Premdass, and M.D. Cohen. 1999. Short-term, low-dose inhalation of ambient particulate matter exacerbates ongoing pneumococcal infections in *Streptococcus pneumoniae*-infected rats. *Proceedings of Third Colloquium on Particulate Air Pollution and Human Health.* 8-94-8-104.
16. **Zelikoff, J.T.** Woodsmoke, kerosene emissions, and diesel exhaust emissions. In: *Pulmonary Immunotoxicology* (M.D. Cohen, **J.T. Zelikoff**, R.B. Schlesinger, Eds.), Klewar Publ., MA. pp. 369-387 (2000).
17. Schlesinger, R.B., LC. Chen, and **J.T. Zelikoff.** 2000. Sulfur and nitrogen oxides. In: *Pulmonary Immunotoxicology* (M.D. Cohen, **J.T. Zelikoff**, R.B. Schlesinger, Eds.), Klewar Publ., MA. pp. 337-353.
18. **Zelikoff, J.T.**, E. Carlson, E., Y. Li, A. Raymond, and J.R. Beaman. 2002. Immune system biomarkers in fish for predicting the effects of environmental pollution. In: *Proceedings of the Fourth Princess Chulabhorn International Science Congress.*

Chemicals in the 21st Century/Chemicals for Sustainable Development. (Chulabhorn Research Institute, Ed.), Trinity Publishing Co., Ltd., Bangkok, THAILAND, pp. 34-56.
19. Duffy, J., and J.T. **Zelikoff.** 2005. Approaches and models for the assessment of chemical-induced immunotoxicity in fish. In: *Investigative Immunotoxicology.* (H. Tryphonas, M. Fournier, B.R. Blakley, J.E. Smits, P. Brousseau, Eds.),Taylor and Francis, NY. pp. 49-63.
20. Zelikoff, J.T. 2005. Trace metals and the immune system. In: *Encyclopedic Reference of Immunotoxicology.* (H.W. Vorh). Springer-Verlag, Germany pp. 340-345.
21. Carlson, E. and **J.T. Zelikoff.** 2008. Fish immunology. In: *Toxicology of Fishes* (D. Hinton and R. Di Giulio, Eds.), CRC Press. pp. 340-352.
22. Ramanathan VM., Agrawal M., Akimoto H., Aufhammer S., (and 34 others), Zelikoff JT. UNEP: Atmospheric Brown Cloud: A Regional Assessment Report with Focus on Asia. Published in Bangkok by United Nations Environmental Program (2008).
23. Ng, SP., K. Yoshido, and **J.T. Zelikoff**. *2010.* Host resistance tumor challenge assays. In: *Techniques in Immunotoxicology (R. Dietert, Ed.) Informa Press.*
24. **Zelikoff, J.T**. 2010. Other environmental health issues: Inhaled woodsmoke. In: *Encyclopedia of Environmental Health*. J. Nriagu (Ed.). Elsevier, UK. Pages 310-330.
25. Mudipalli, A. and **Zelikoff, J.T.** (Eds). Essential and non-essential metals: carcinogenesis, prevention and therapeutics. Springer, UK. 2018.
26. Ng, S.P**., Zelikoff J.T.** Tumor challenges in immunotoxicity testing. Vol. 599. Humana Press, Springer Science. Immunotoxicity Testing: Methods and Protocols, Methods in Molecular Biology. (2018)
27. **Zelikoff, J.T.**, and M.D. Cohen. Pulmonary Immunology. In: *Comprehensive Toxicology*. (C. McQueen, Ed.). Elsevier, UK. 2018.

INVITED NATIONAL AND INTERNATIONAL LECTURES/PRESENTATIONS (Present – 2000, *in descending order***):**

August 2018: International Society of Exposure Science (ISES); International Society for Environmental Exposure (ISEE). *Contamination of the Ramapough Nation: A toxic legacy.* **Environmental contamination and Indigenous populations symposia.** Ontario, Canada.

February 2018: Louisiana State University. Electronic cigarettes and pregnancy: Lessons learned from mice. Baton Rouge, LA

January 2018: Mt. Holyoke College. What's safer for the unborn child: electronic cigarettes or air pollution? MA.

December 2017: Texas A & M. Prenatal exposure to ambient particulate matter impacts cardiovascular development. TX.

December 2017: International Conference on Environmental Impacts. Air pollution and pregnancy. Deradun, India

November 2017: International Conference on "Impact of Environment on Women's Health: **Amity University Uttar Pradesh**. Maternal exposure to particulate air pollution during pregnancy and Impacts on fetal health: What are we learning from animal studies? Lucknow, India.

November 2017: **American Public Health Assoc. (APHA) Annual Meeting**. Identifying Environmental concerns, environmental exposures and health concerns in the Ramapough Lenape Tribe. Atlanta, GA.

October 2017: International Society of Exposure Science. A community in toxic crisis: Ramapough Native Americans. Durham, NC.

April 2017: Queensborough College. Neurocognitive effects of E-cigarettes. Queens, NY.
July 2016: NIOSH seminar. Reproductive implications of Nanomaterials. WV
July 2016: EPA seminar. Ambient particulate matter and cardiotoxicity. Chapel Hill, NC.
June 2016: Workshop on Nanomaterials and the fetal-placental unit. Prenatal Nephrotoxicity and Maternal Nanomaterial Inhalation. Boston, MA.
May 2016: NIH Tobacco Research. Toxicological assessment of smokeless tobacco products: A systematic ranking system. Bethesda, MD
April 2016: AHA, ATrac Meeting. Toxicity ranking of alternative tobacco products. Louisville, KY.
March 2016: Society of Toxicology: Course in Medical Education. Effects of fracking on reproductive and developmental health. New Orleans, LA
March 2016: Society of Toxicology: Symposia on Fracking and Health. Effects of fracking on reproductive and developmental health. New Orleans, LA
February 2016: American Association for Advancement of Science: Symposia on Alternative Tobacco Products and Health. Early life exposure to alternative tobacco products as a major risk factor of later life chronic disease. Washington, DC
October 2015: 7th International Symposia on Nanotechnology and Occupational and Environmental Health. Reproductive and developmental toxicity of gold nanoparticles in a mouse model of pulmonary exposure. Limpopo Province, South Africa.
May 2015: Amer. Assoc. Immunol. Maternal inhalation of ambient particulate matter causes alterations in immune profiles and anti-tumor mechanisms in juvenile murine offspring. New Orleans, LA.
April 2015: Wayne State University, *CURES Seminar Series at Wayne State University's Institute of Environmental Health Sciences*. Maternal exposure to particulate air pollution during pregnancy impacts fetal development and neonatal growth in a mouse model.
March 2015: **Society of Toxicology**. Symposia on: New and Emerging Tobacco Products—Biomarkers of Exposure and Injury (Chair). Reproductive/Developmental effects of exposure to new and emerging tobacco products and to nicotine delivery devices in a mouse model. San Diego, CA.
Dec. 2014: University of Illinois – Maternal exposure to ambient particulate matter during particular gestational windows produce developmental and reproductive consequences in a mouse model. Urbane, IL.
July 2014: Oregon State University – Early life nanoparticle exposure brings early and later life health consequences. Corvallis, OR.
March 2014: Society of Toxicology – Tobacco products and prenatal exposures. Phoenix, Arizona.
February 2014: ***West African Society of Toxicology*** – Air pollution in developing nations. Lagos, Nigeria.
January 2014: ***Ernst Strungmann (ES) Forum, (Rapporteur)-*** *Heavy metals and infectious disease.* Frankfurt Germany.
November 2013: American Chemical Council. Risk Assessment and Communication, Working Group. Washington, DC.
October 2013: ***First International Conference on Waterpipe Tobacco Research.*** Working Discussion Group Leader: Abu Dhabi.
October 2013: ***NIH-sponsored Workshop in South Asian Diversity Populations and Health Effects.*** Sloan Kettering Cancer Center. Working Group member on smokeless tobacco. NY, NY.

June 2013: ***FDA, Center for Tobacco Control***. Public health impacts of fetal exposures to tobacco & environmental toxicants: From early life to adult disease and policy needs. MD

March 2013: ***Society of Toxicology, Committee on Diversity Initiatives*** – Exposure to smoked and smokeless tobacco *in utero*: Fetal injury and life long consequences. San Antonio, TX

February 2013: ***Nigeria University*** – Smokeless tobacco: A global look at the problem, Port Harcourt, NIGERIA

February 2013: ***FDA: Center for Medical Devices*** – Fetal basis of adult disease: early life exposure to environmental and occupational toxicants. Silver Spring, MD.

October 2012: ***Memorial Sloan Kettering*** – Arsenic contamination in Bangledesh. New York, NY

May 2012: ***Memorial Sloan Kettering*** – Toxicology of Smokeless tobacco. NY, NY.

April 2012: ***University of Connecticut*** – Tobacco products *in utero* are associated with later life disease outcomes. Storrs, CT.

March 2012: ***Biomass Symposium*** – Toxicological implications for domestic burning. Feb. 2012: **NYU Medical Center, Dept. of Psychiatry** - Chemical stressors *in utero* and later life disease outcomes. New York, NY.

Jan 2012: *British American Tobacco –* *In vitro* translational studies and the toxicology of smoking. Southampton, UK.

Dec. 2011: FDA – ***The reproductive effects of cadmium nanoparticles***. Reston, VA.

Dec. 2011: **NYU Dept. of Bioethics** – Cigarette smoking & smokeless tobacco: Is there really a good choice? New York

Oct. 2011: NorCal SOT **– Fetal basis of adult disease – the role of maternal smoking**. Menlo Park, CA.

Sept. 2011: ***European Aerosol Conference – Plenary Lecture*:** The toxicology of biomass combustion emissions. Satellite Workshop on Biomass Combustion, Manchester, England.

March 2011: ***NYU Ethics Forum*** - Exposure to Cigarette Smoke *in Utero*: Fetal injury and Life Long Consequences**.** New York

March 2011: *NYU Medical Center, Dept. of Obstetrics and Gynecology Grand Rounds* – Early life insult by tobacco smoke and later life disease susceptibilities. March 15, 2011

March 2011: *Society of Toxicology, Committee for Diversity Interests* – Cigarette exposure *in utero*: You are what you breathe. Washington, DC. March, 2011.

Nov. 2010: *Texas A & M University –* Early life exposure to cigarette smoke suppresses anti-tumor immune defenses of the prenatally exposed offspring in a mouse model" College Station, TX.

May 2010: ***Workshop on Emissions and Health Impacts of Biomass Fuels*** – Health effects of woodsmoke: A toxicological model for mechanisms and policy needs. Penn State, State College, PA.

March 2010: ***Environmental and Occupational Health Sciences Institute, Rutgers University*** - Fetal exposure to cigarette smoke mediates anti-tumor immune mechanisms in adult murine offspring. New Brunswick, NJ. March, 2010.

March 2010: ***Society of Toxciology, Committee for Diversity Interests –*** Exposure to cigarette smoke in utero: Fetal injury and life-long consequences. Salt Lake City, UT.

Nov. 2009: *United Nations Environmental Programme –* Toxicological assessment of the atmospheric brown cloud. Incheon, Korea.

Sept. 2009: *7th Congress of Toxicology in Developing Countries* – Fetal insult and later onset diseases. Sun City, South Africa.

August 2009:***Japanese Society of Immunotoxicology*** – Prenatal exposure to cigarette smoke increases tumor susceptibility of juvenile mice via changes in anti-tumor immune mechanisms. Asahikawa, Japan.

May 2009: *Asia-Pacific Forum on Andrology*, Hormonal changes accompanying cigarette smoke induced preterm births in a mouse model. Nanjing China.

Dec. 2008: ***St. Johns University*** – Mechanistic insights into offspring cancer risk associated with maternal smoking. Queens, NY.

August 2008: *U.S. EPA, National Center for Environmental Assessment* - Gender-related effects on offspring tumor risk and response to prenatal cigarette smoke exposure may be related to testosterone: a toxicological model. Washington, DC.

June 2008: *Institute for Science and Health (IFSH)* – Early exposure to cigarette smoke may serve as an indicator of chronic diseases in the offspring later in life. Cardiff, Wales.

March 2008: *Society of Toxicology* –Prenatal exposure to tobacco smoke induces asthma-related responses in non-sensitized female offspring later in life. Seattle, Washington.

March 2008: *Society of Toxicology* – Prenatal exposure to cigarette smoke: Are our children paying the price? Seattle, Washington. March 2008.

August 2007: *United Nations Environmental Program (UNEP)* – Toxicology of the Atmospheric Brown Cloud (ABC). Seoul, Korea.

March 2007: *University of Louisville (KY)* – Increased cancer risk: A possible birth defect associated with maternal smoking. Louisville, KY.

March 2007: *Institute for Science and Health (IFSH)* – Prenatal cigarette smoke exposure and offspring asthma. Louisville, KY.

Feb. 2007: ***International Conference on Environment: Survival and Sustainability* -** Sustaining a healthy fetal environment: A little told threat of increased cancer and asthma risk for the juvenile offspring exposed prenatally to cigarette Smoke. Near East University, Nicosia-Northern Cyprus.

Feb. 2007: *International Conference on Environment: Survival and Sustainability* - Contamination of aquatic environments with polychlorinated biphenyls (PCBs) or benzo(a)pyrene (B[a]P) can adversely impact the immune health and sustainability of inhabiting Fish. Near East University, Nicosia-Northern Cyprus.

Dec. 2006: *Philip Morris External Review Symposia* – Effects of prenatal exposure to cigarette smoke on tumor development and immune surveillance mechanisms in the developing offspring: A toxicological model. Landsdowne, VA. Dec. 2006.

May 2006: ***MidAtlantic Chapter of Society of Toxicology (MASOT)*** – Increased cancer risk in the offspring: A birth defect associated with maternal smoking. Scotch Plans, NJ.

April 2006: ***University of Guelph*** – Maternal smoking and cancer: Are the unborn children paying the price? Kempville, Ontario Canada.

March 2006*: Institute for Science and Health* – Prenatal exposure to mainstream cigarette smoke alters susceptibility of the offspring to asthma. Vienna, Austria.

March 2006: *Society of Toxicology* – Maternal smoking and cancer: Are the unborn children paying the price? San Diego, CA.

October 2005: *Chulabhorn Research Institute* – *Immunotoxicology: A new focus for Thai science.* Scientific Research Institute of Thailand. Bangkok, Thailand.

May 2005: ***American Thorasic Society* -** Immunotoxicological mechanisms of prenatally-exposed respiratory contaminants. Symposia on “Impact of prenatal and early infancy environmental exposures on neonatal and infant health”. San Diego, CA..

May 2005: ***California Society of Environmental Toxicology and Chemistry –*** Mechanisms of Fish Immunotoxicity. Berkley, CA.
April 2005: ***Life Science Research Organization (LSRO)*** **–** Prenatal exposure to cigarette smoke increases tumor susceptibility in the offspring: A toxicological model. St. Louis, MO.
March 2005 - ***Society of Toxicology*** – Immunotoxicity of prenatal mainstream cigarette smoke exposure. Symposia on "Mechanisms Linking the Lung and Immune System". New Orleans, LA.
Feb. 2005: ***Institute for Science and Health (IFSH)*** – Effects of in utero cigarette smoke exposure on asthma development in the offspring. Washington, DC.
Feb. 2005: ***Canadian Lung Association*** – Health Effects of Woodburning. New Brunswick, Canada.
Nov. 2004: ***Environmental Mercury Research Forum*****.** Metal toxicity in aquatic organisms. Energy & Environmental Research Center (U. of North Dakota). Grand Forks, ND.
Oct. 2004: ***VIIth Annual Conference of Soil, Sediments and Water*****.** Immunological Alterations as Bioindicators of Environmental Health. Amherst, MA.
Sept. 2004: ***Slovenian Society of Toxicology*** – Immunological biomarkers. Lublijana, Slovenia.
March 2004: ***Society of Toxicology*** **–** Inhalation of concentrated ambient particulate matter and associated metals increases host susceptibility to pulmonary pneumonia. Baltimore, MD.
Jan. 2004: ***University of Arizona*** **–** Toxicological impact of inhaled wood smoke on pulmonary antimicrobial defense. Tucson, AZ.
Jan. 2004: ***College of Staten Island*** **–** Toxic insult and human health effects: Lessons learned from an aquatic species. Staten Island, NY.
Dec. 2003: Sixth National Environmental Public Health Conference (Center for Disease Control) Woodsmoke: A closer look at public health concerns and mechanisms of toxicity. Atlanta, GA.
Nov. 2003: ***Society of Environmental Toxicology and Chemistry*** **-** Immunotoxicology and Risk Assessment. Austin, TX.
Oct. 2003: ***Chulabhorn Research Institute*** **–** Immunotoxicology Course Series (10d). Bangkok, Thailand.
June 2003: ***International Symposium on Pharmaceutical Sciences*** **-** Health Effects of Inhaled Particulates. University of Pharmaceutical Sciences. Ankara, Turkey.
June 2003: United States Army Center for Environmental Health Research - Immune Assays for Hazard Assessment and Species Extrapolation. Fort Detrick, MD.
May 2003 - ***Pollutant Responses of Marine Organisms (PRIMO)*** **-** Immunotoxicology in Fish. Tampa, FL.
March 2003: ***Society of Toxicology*** - Woodsmoke: Cozy Atmosphere or Public Menace? Salt Lake City, UT.
Nov. 2002: ***Society of Toxicology and Chemistry*** **-** Immune Biomarkers for Use in Ecological Risk Assessment. Salt Lake City, UT.
Oct. 2002: ***Padova University*** **-** Lessons Learned About Human Health From Aquatic Species. Padova, Italy.
Oct. 2002 - ***Slovenia Society of Toxicology*** **-** Biomarkers for Ecotoxicology. Ljubljana, Slovinia.
Sept. 2002: ***University of Florida*** **-** Effects and Mechanisms of Benzo(a)pyrene-induced Immunosuppression in Fish. Gainsville, FL.

June 2002: ***Yale University, Dept. of Occupational and Environmental Medicine -*** Lessons on Human Health and Toxic Impact Learned from our Aquatic Counterparts.
Sept. 2001: *Third International Meeting on Molecular Mechanisms of Metal Toxicity and Carcinogenicity* - Immunodysfunction: An underlying Mechanism of Metal Toxicity in Aquatic Organisms. Sardinia, Italy.
July 2001: ***Pollutant Responses in Marine Organisms* -** Immunotoxicology in fish - Applications and Mechanisms of Response. Plymouth, England.
Oct. 2000: *Conference on Women in Science* - Aging: Good or Bad News for the Immune Response. Rutgers University. New Brunswick, NJ.
Oct. 2000: *International Conference on Environmental and Occupational Lung Disease* - Woodsmoke Impairs Host Resistance Against Pulmonary Infections in an Animal Model. Lucknow, India.
May 2000: *EPA-Duluth* - Fish Immune Status: A Sensitive System for Assessing Toxicological Impact of Aquatic Environments. Duluth, MN.
May 2000: *University of Minnesota-Duluth* - Processes and Mechanisms of Woodsmoke-induced Immunosuppression. Duluth, MN.
March 2000: **International Symposia on Medaka -** Japanese Medaka: A Sensitive Teleost Model for Assessing the Immunotoxic Effects of Potential Endocrine-Disrupting Chemicals. Osako, Japan.
Nov. 2000: *The Fourth Princess Chulabhorn Science Congress*- Immune System Biomarkers for Predicting the Effects of Environmental Pollution. Bangkok, Thailand.

EDITOR/EDITORIAL BOARD APPOINTMENTS

Editor and Co-Editor:

Metal Toxicology, Co-Editor (Springer Publ.) – (2016)
Pulmonary Immunotoxicology (Klewar Publ.) - (2000)
Immunotoxicology of Occupational and Environmental Metals. (Taylor and Francis) - (1998)
Ecotoxicology: Responses, Biomarkers and Risk Assessment. (SOS Publications) - (1997)
Modulators of Immune Responses: A Phylogenetic Approach - Vol. 2 (SOS Publications)-(1996)
Modulators of Immune Responses - Vol. 1 (SOS Publications) - (1994)
Toxicology and Ecotoxicology News (Taylor & Francis) - (1995-1998)
Book series on: Ecotoxicology (John Wiley & Sons) - (1995-1997)

Associate Editor-

Open Journal of Immunology (2015-2018)
Journal of Developmental Origins of Health & Disease (2012-2013; Themed Editor)
Journal of Toxicology and Applied Pharmacology – (2005-2014)
Journal of Toxicology and Environmental Health - Part A - (2001 - Present)
Biomarkers: Exposure, Effects and Susceptibility - (1995 – 2007)

Editorial Advisory Board-

Envronmental Health Perspectives (2017-2020)
Open Journal of Toxicology (2015-present)
Inhalation Toxicology (2015-present)
Open Journal on Immunology (2009-present)
Journal of Immunotoxicology (2004 - 2016)

Toxicol. Sci. (2007-2016)
Toxicology (1997- 2016)
Environmental Health Perspectives (2009 – 2013; named a top reviewer for 2011)
Environmental Bioindicators (2005- 2011)
Inhalation Toxicology (2004 – 2008; 2013-2016)
Fish and Shellfish Immunology (1997 - 2008)
Toxicology Applied Pharmacology (1996 - 2005)
Diseases of Aquatic Organisms (1995 - 2006)
Aquatic Toxicology (1998 - 2006)
Journal of Toxicology and Environmental Health (1996 - 2001)
Fish Immunology Technical Communications- Vols. 2-5 (1994 - 1997)

CHAIRED SESSIONS/MEETING ORGANIZER (1997 – present, descending order)
<u>*Outside University*</u>

o Organizer/Instructor of International Student & Faculty Workshop on "Fish Immunology" (Tasmania, Australia; February 1997)
o Organizer/Instructor of Student & Faculty Mini-workshop on "Fish Immunology" (Christ Church, New Zealand; February 1997)
o Chairperson at International Meeting on "Developmental and Comparative Immunology" (Williamsburg VA; July 1997)
o Organizer of Student & Faculty International Workshop on "Fish Immunotoxicology Techniques" (American College, Madurai India; February 1999).
o Organizer of Continuing Education Course on "Exposure Assessment: Methods and Applications" at Aquatic Toxicity Workshop Meeting (Edmonton, Canada; October 1999).
o Chairperson of Symposium on "Profiling Immunotoxicology" at Aquatic Toxicity Workshop Meeting (Edmonton, Canada; October 1999).
o International Conference on Environmental and Occupational Lung Disease (Lucknow, India; October, 2000)
o Symposium Coordinator/Chairperson at Society of Toxicology (1993, 1994, 1996-1999; 2005-2009)
o Continuing Education Coordinator/Chairperson at Society of Toxicology (1994, 1995, 2000, 2001)
o Slovenian Society of Toxicology (Nova Gorcia, Slovenia; September 2004, 2005)
o Aerosol Dynamics and Health: Strategies to Reduce Exposure & Harm. (Chairperson, Public Health Issues Involving Environmental & Tobacco Aerosols; Cardiff, Wales 2008)
o SOT - Co-Chair, Symposia and Continuing Education Course, 2009, 2010, 2011, 2015, 2016, 2018, 2019
o ISEE/ISES – co-Chair, Symposia on Environmental Contamination and Indigenous populations. (Ontario, Canada, 2018)

<u>FEDERAL & STATE ADVISORY BOARDS/PANELS/REGULATORY AGENCIES (Contributions to Regulatory Guidelines)</u>

2018-2019: New York City Housing Authority, Advisory Board member for "Healthy Homes".

2017-2018: National Academy of Science, Engineering, Medicine –
-Board on Earth Sciences & Resources; Board on Environmental Studies & Toxicology; Board on Health Sciences Policy: Potential Human Health Effects of Surface Coal Mining Operations in Central Appalachia. 2017-2019.

2015: European Respiratory Society and Environment and Health Committee for American Thoracic Society. Position paper participant on "What constitutes an adverse health of air pollution?" Brussels, BE, March 2015.

2013: American Chemistry Council's Center for Advancing Risk Assessment Science and Policy (ARASP) Workshop - Informing Risk Assessment: Understanding and Communicating Uncertainty in Hazard Assessment. (2013)

2011: Department of Defense
- Gulf War Illness Peer Review Panel (2011)

2013: FDA, Tobacco Control Division, Advisory Consultant (2013)

2013-2006: NASA
- Lunar Dust Exposure Standard Review Panel (2013)
-Lunar Science Institute, Moon Science Grant Review Panel (2008)
- Lunar Dust Non-Advocate Review Panel (Chair, 2006-2008)

2002-2012: National Academy of Science
- National Research Council (NRC): Committee on Low Level Lead in Ammunition (2011 – 2012)
- National Research Council (NRC): Peer Review of NRC Report on Acute Exposure Guideline Levels (2010)
- Institute of Medicine (IOM): Peer Review of IOM Report on Depleted Uranium final document (2008)
- National Research Council (NRC) - Committee on Toxicology/Subcommittee on Spacecraft Water Exposure Guidelines (2001 - 2008)
- Institute of Medicine (IOM): Committee on Gulf War and Health - Part 3 (2002 – 2004)
- Institute of Medicine (IOM): Reviewer for Agent Orange final document (2003)

2012-2010: National Toxicology Program, Science Advisory Board (2010-2012)

1996-2017: National Institute of Health (NIH) & National Institute of Environmental Health Science (NIEHS)

NIEHS, Member reviewer for Core Centers (2018)

-NIEHS, Study Section member (2015-2017)

-NIEHS KO1, K99, R23 reviewer (2014, 2015)
-NIEHS K01, K99 Awards member (2013)
-NIEHS Immunotoxicology Center Program (2012, 2013)
-NIEHS Oceans Centers (2012)
- NIEHS Just-in-time Grants (**Chair,** 2012)
- NIH College of Scientific Reviewers (2010 – 2013)
- NIH Integrative & Comparative Endocrinology (2011)

- NIEHS Time Sensitive Grant (**Chair;** 2010)
-NIEHS P30 (NIEHS Centers of Excellence), (2008, 2009)
- NIEHS Challenge Grants, (2009)
- NIEHS K01 grant applications, (2008)
- NIH Innate Immunity and Inflammation (III) Study Section Full Member, (2005 – 2007)
- NIEHS Program Project grants, *(2006)*
- NIEHS ALTX – 4 (Alcohol and Toxicology) Study Section Full Member, (1996 – 2000)

2005: National Institute of Environmental Health Sciences (NIEHS) & U.S.EPA & NASA
- Expert Panel on "Global Earth Observations: Application to Air Quality and Human Health" (2005)

2005: National Institute of Allergy & Infectious Disease (NIAID) & Department of Defense (DOD)
- Expert Panel Workshop on Pulmonary Threat Agents (2005)

2013-210: New Jersey Department of Environmental Protection
- Human health Committee (2010 – 2013)
- Soil Standards Sub-committee (2010 – 2011)
- Aerosol Sub-committee (2011 – 2012)

2011-2011: United Nations Environmental Program (UNEP) Steering Committee (2006 – 2011)
- Atmospheric Brown Cloud Human Health Panel

2004-2005: U.S. EPA Science Advisory Board & Review Panel
- Metals Risk Assessment Framework Review Panel, (**Co-Chair** of Human Health Breakout Group, 2004 – 2005)
- Nanoparticle Review Panel (2005)

APPOINTMENTS/ELECTED OFFICES
Society of Toxicology (SOT)

Nominating Committee (2018-2020)
Committee for Diversity Initiatives (2014-2015, member; 2015-2016, Co-chair; 2015-2016; Chair, 2016--2017)
Board of Councilors (2011 – 2014**; Secretary-elect**, 2011-2012; **Secretary**, 2012-2014)
Nominating Committee (2007 - 2009)
Congressional Representative (2004 – 2005)
Education Committee (2002 – 2005; **Chair**, 2004 – 2005)
Education Sub-Committee for Minority Initiatives (2001 - 2004; **Chair**, 2003-2004)
Continuing Education Committee (1998 - 2001; **Chair,** 1999 - 2000)
Program Committee (1995-1998)

Inhalation & Respiratory Specialty Section
Councilor (2017-2019)

Ethical and Legal Specialty Section

President (2017-2018)
VP-elect (2016)

Immunotoxicology Specialty Section
President (1999-2000)
Vice-President (1998-1999)
Secretary/Treasurer (1995-1997)
Program Committee (1993-1999)
Awards Committee (1993, 1998, 2000)
Education Committee (Chair, 1992-1996; 2004-2009)
Nominating Committee (1998 - 2001, Chair, 1999-2000)
Councilor (2000-2001)

Metals Specialty Section
President (2003-2004)
Vice President (2002-2003)
Awards Committee (**Chair,** 2001 - 2004)
Program Committee (**Chair**, 2001 - 2004)
Nominating Committee (2001 – 2004, **Chair**, 2001-2003)

MidAtlantic (Chapter) Society of Toxicology (MASOT)
Nominating Committee (2009 [**Chair]**, 2010, 2011)
Past president, Councilor (2009-2010)
President (2008-2009)
Vice President (2007-2008)
Vice President-elect (2006-2007)
Councilor (2001 - 2004)
Program Committee (2000 – Present; Chair 2006-2007)

NYU Langone School of Medicine
Faculty Council Representative (2010-2019; Vice President 2011-2012, 2014-2015);
Benefits and Tenure Sub-committee (2015-2016)
Academic Affairs Sub-committee (Chair, 2012-Present)
Basic Science Sub-committee (co-Chair, 2017-2019)
IACUC Review Board (2009-2011; 2017-2019)
Grievance Committee (2017-2020)
NYU Senate (alternate; 2018-2021)

Department of Environmental Medicine
Promotion & Tenure Committee (2008-2014; **Chair**, 2010-2012)
Search Committee (2010-2013)
Biological Safety Committee- (**Chair**, 1990-1999)
Graduate Steering Committee (1999- 2014; Interim **Co-chair** 2001-2002)
Toxicology Masters' Program (Director, 2002 – 2008; **Co-director**, 2008-2011)

GRANT REVIEWER *Ad hoc* (Federal [Non-NIH]/State/Private):
Federal
Scandanavian Research Program (2013, 2016)
NASA, Moon dust program (2008)
Canadian Centers for Research (2000 – 2004)
DOD (*Ad hoc,* 1999 - present)

EPA (*Ad hoc,* 2002 - present)
Natural Sciences and Engineering Research Council of Canada (*Ad hoc,* 2002 – present)

State/Private
Center for Indoor Air Research
Environmental and Occupational Science Health Inst. (Rutgers U.)
IFS Research Grants for Developing Nations
Johns Hopkins Pilot Projects
Michigan Sea Grant
New Jersey Sea Grant
New York Sea Grant
Philip Morris Foundation

ADJUNCT APPOINTMENTS, CONSULTING, ADVISORY BOARDS

- **Weill Cornell Medical School** (NY, NY) – External Advisory Board for NIH Diversity Grant (2013-2015)
- **Chulabhorn Research Institute & University** (Bangkok, Thailand) **-** Adjunct Professor (2003-present)
- **Cornell University, Inst. for Comparative and Environmental Toxicology** (Ithaca, NY) - Adjunct Professor (1996-2005)
- **American Lung Association** - Criteria Document on Woodsmoke (2001)
- **Fish and Wildlife Services** - Status of the Hudson River (2000)
- **International Life Sciences Institute** - Research strategy on age-related differences in susceptibility (1998)
- **Stratus Consulting Inc. -** Assessment of PCB-contaminated sites (1997 - 2000)

U.S. EPA - Criteria document on the immunotoxicity of endocrine disruptors (1997)

MENTORING ON A GLOBAL LEVEL (6)

- Juliet Igbo (Doctoral student co-mentor – U. of Lagos, Nigeria – 2015-2019)
- Anishka Lewis (Masters student- Jamaica – 2014)
- LeighAnn Koekemoer (Masters student – South Africa-2014)
- Dr. Orish Orisakwe – University of Port Harcourt, Nigeria – 2013-present)
- Dr. Hari Jott Dosih (Nepal Health Research Council – Kathmandu, Nepal- 2014-present)
- Dr. Chanthana Tangjarukij (Chulabhorn Research Institute – Bangkok, Thailand-2012-present)

STUDENT & JUNIOR FACULTY MENTORING

Research Advisor:

***College and High School* (15)**

- Aaron Asiedu-Wiafe (2017-2018; Monroe-Woodbury High School, Monroe, NY)
- Aastha Parikh (2016-2017; Monroe-Woodbury High School, Monroe, NY)
- Daniel Smith (2013-2014; Fairlawn High School, Fairlawn, NJ)
- Alejandro Jorge (2012; Ramapo College, NJ)
- Eric Bloom (2011-2012; Highland Mills High School [Highland Mills, NY])
- Sujay Avencar (2009-2011; Suffern High School [Suffern, NY])
- Sam Openheim (2009-2011; Suffern High School [Suffern, NY])
- Monica Feldman (2007-2009; Spring Valley High School [Spring Valley, NY])

- George Markt (2005-2009; Ramapo High School [Ramapo, NY])
- Payal Roy (2006 – 2007; New York University [NY, NY])
- Rebecca Kurtzman (2005 – 2007; Spring Valley High School [Spring Valley, NY])
- Erica Stone (2006, Ramapo College [Mahwah, NJ])
- Elizabeth Nadziejko (2000; Washingtonville High School [Washingtonville, NY[)
- Kevin Hazard (1999 – 2000; Spring Valley High School [Spring Valley, NY])
- Songeeta Pachachuria (1997-2000; Spring Valley High School, [Spring Valley, NY])
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<u>Post-Baccalaureate (2)</u>
- *Parnavi Desai* (2015-present; NYU, Biology)
- *Tomas Dunne* (2014-2015; Penn State)

<u>Masters</u> **<u>(30)</u>**
- Arianna Schwartzer (2017-2019; NYU Environ. Health Sci)
- Kathryn Fetce (2016-2018; NYU Environmental Health Sciences)
- Nicholas Lawrence (2016-2018; NYU Environmental Health Sciences)
- Alexander Lucca (2017-2018; NYU Biology)
- Annie J.Thaikkatil (2016-2017; NYU Biology)
- Leena Babiker (2017-2018; NYU Biology)
- Patricia Costa (2014-2016; NYU Environ. Health Sci
- Maria Putilina (2013-2014-NYU, Biology)
- Kirtan Kaur (2013-2015)
- Sarah Attreed (2013-2015)
- Sabina Sutjec (2013-2014-NYU, Biology)
- Kaitlyn Koenig (2012-2014)
- Heather Larkin (2012-2013-NYU, Biology))
- Dana Lauterstein (2011-2013) – 2 SOT student awards (2013)
- Yi-Chuh Chen (2010-2011 Incomplete-NYU Biology)
- Ya-Chien Yu (2010-2011-IncompleteNYU Biology)
- Yuan-Chun Hsiao (2010-2011-Incomplete NYU Biology)
- Lauren Rosenblum (2009-2011-NYU Biology)
- Sandra Perella (2008-2010)
- Kotaro Hoshido (2007-2009-NYU Biology)
- Jacqueline Grabowski (2006-2008)
- Elizabeth Vanza (2004 – 2006) – *SOT student award (2006)*
- Elizabeth Berg (2003 - 2005)
- Shannon Doherty (2002 - 2005)
- Colette Prophete (1998 - 2001)
- Jessica Duffy (1999 - 2001)
- Migali Jorge (1998 - 2000)
- Cheryl Premdass (1998 - 2000)
- Andrea Raymond (1997 - 2000) – *1 SOT award*
- Thomas McManus (1994 – 1996, Co-advisor)

Doctorate **(9)**

- Pamela Tijerna (2013-present) – *SOT CDI award (2014); SOT (1st place Hispanic Organization of Toxicology, 2015); SOT(Mary Amdur Inhalation Fellowship, 2015)*
- Dana Lauterstein (2013-present)- SOT (Safety Assessment Specialty Section, 2015)
- Juliett Igbo (2015-2016), Co-Advisor (U. of Lagos, Nigeria)
- Sheung Pui Ng (2004 - 2010) – *9 SOT student awards including Novartis Achievement Award (2008-2010)*
- Jessica Duffy (2001 – 2007) – *2 SOT awards (2004); 3 SETAC awards (2004, 2005, 2006)*
- Chanthana Settachan (Co-Advisor; 2003 – 2009; Chulabhorn Research Institute, Bangkok Thailand)
- Erik Carlson (1999- 2003) – *1 SOT award (2000)*
- Ninah Enane (Co-Advisor, 1995 - 1999)
- Peter Atkins (Co-Advisor, 1992 - 1996)

Post-doctoral Trainees **(2) & Mentoring Committees**

- Jason Blum (2009 – 2012) – *1 SOT post-doc award*
- Daniel Willis (2011 – 2013)- NSF/FDA post-doctoral fellowship (Zelikoff, PI)- 2013

Junior Faculty Mentoring Committee **(2)**

- Jason Blum (2012 – Present)
- Kevin Cromar (2012-Present)

<u>Doctoral Thesis Committee</u> <u>(12):</u>

- Kirtan Kaur (2016-2018, Chair)
- Carolyn Klocke (2015-2017) – University of Rochester (External Examiner)
- Mary Francis (2015-2016) - Rutgers University (External Examiner)
- Eric Saunders (2012-2015)
- Joshua Vaughn (2012 – 2015)
- AJ Cuevas (2007 – 2012)
- Jessica Lyon (2007 - 2012)
- Judy Blatt Nichols (Chair, 2007 – 2011)
- Patricia Gillespie (2006 - 2010)
- Elizabeth Vanza (Chair, 2004 – 2009)
- Ann Zulkosky (2005 – 2007; SUNY Stony Brook)
- Samantha DeLeon (Chair, 1999 – 2003)

COMMUNITY OUTREACH, EDUCATION & ENGAGEMENT INITIATIVES:

- ***Director***, *Community Outreach & Education Program, NYU, Dept. of Environ. Med.* (2005- present)
- ***Director***, *NIEHS Center of Excellence, Community Outreach & Engagement Program, NYU, Dept. of Env. Med. (2005 – present)*
- ***Director,*** *NIEHS Superfund Community Outreach and Education Core, NYU, Dept. of Environ. Med.* (2005- 2010)

- ***Co-director***, NIEHS Superfund Translation Core, *NYU, Dept. of Environ. Med.* (2005- 2011)

  Community Partners:
  - *Ironbound Community Corporation (ICC): Newark, NJ (2015-present)*
  - *Ramapough Lenape Tribal Nation: Ringwood, NJ/Mahwah, NJ/Hillburn, NY (2013-present)*
  - *City of Garfield, NJ (2012-present)*
  - *Susquehanna, PA: Fracking communities (2015-2016)*
  - Flint, Michigan via Water Defense

Translation/Communication of toxicology to non-toxicologists & underserved minorities

- Community groups in PA and NY: Environmental and Health Implications of Hydraulic Fracturing (2013-2014).
- Ramapo Indians: Living on a Superfund Site (2014-present)
- NY Presbyterian Lang Program for Underserved Youth (2010 - Present)
- *Harlem Children Society Mentoring Program - Bronx, NY* (2010-Present)
- Y-2 Kids (NY State 4th – 12th grade, Career day representative, 2008 - Present)
- *Center for Talented Youth, New York University Department of Environmental Medicine & Johns Hopkins Center for Talented Youth (2005 – Present)*
- *Environmental Commission of Ramsey (2001 – 2007; Vice-Chair; 2004-2006)*

- Ramsey, New Jersey. Woodburning: A Cozy Atmosphere or a Public Menace? (2003)

- *Senior Citizen Advisory Board of Ramsey* (2003 - 2005)
- *Ramsey High School (Presenter on toxicology and the environment 2005-2006)*
- *Youth Guidance Commission of Ramsey* (1999 - 2001)
- *Rotary Club*, Goshen, New York. Woodburning: A Cozy Atmosphere or a Public Menace? (2003)
- *Upper Saddle River Community Center*, Upper Saddle River, New Jersey. The Hazards of Woodburning (1997)

Non-Academic Related Outreach Committees:

- 2011- 2014 – *Board of Ethics*, Community Hospice of Bergen County (NJ)
- 2009- 2014 – *Fundraising Committee*, Community Hospice of Bergen County (NJ)
- 2006-2013 – President, Condominium Association
- 2013-2016 – Vice-President, Condominium Association
- 2018 – South Bronx Asthma Coalition

Exhibit B

MATERIALS AND DATA CONSIDERED

Literature

Abraham, J.L., and D.D. McEuen. "Inorganic Particulates Associated with Pulmonary Alveolar Proteinosis: SEM and X-Ray Microanalysis Results." *Appl. Pathol.* 4 (1986): 138-146.

Abubaker, Kalid, Rodney B. Luwor, et al. "Inhibition of the JAK2/STAT3 pathway in ovariancancer results in the loss of cancer stem cell-like characteristics and a reduced tumor burden." *BMC Cancer* No. 14 (2014): 317.

Abubaker, Kalid, Rodney B. Luwor, et al. "Targeted disruption of the JAK2/STAT3 pathwayin combination with systemic administration of paclitaxel inhibits the priming of ovarian cancer stem cells leading to a reduced tumor burden." *Frontiers in Oncology* No. 4(75) (2014).

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Acencio, Milena M. P., Evaldo Marchi, Lisete R. Teixeira, Bruna Rocha Silva, Juliana Sanchez Silva, Carlos Sergio Rocha Silva, Vanessa Adelia Alvarenga, Leila Antonangelo, Francisco Suso Vargas, and Vera Luiza Capelozzi. "Talc Particles and Pleural Mesothelium Interface Modulate Apoptosis and Inflammation." *Pathology* 46, no. S2 (2014): S76.

Akhtar, Mohd Javed, Maqusood Ahamed, M.A. Majeed Khan, Salman A. Alrokayan, Iqbal Ahmad, and Sudhir Kumar. "Cytotoxicity and Apoptosis Induction by Nanoscale Talc Particles from Two Different Geographical Regions in Human Lung Epithelial Cells." *Environmental Toxicology* 29 (2014): 394–406. https://doi.org/10.1002/tox.21766.

Akhtar, Mohd Javed, Sudhir Kumar, et al. "The primary role of iron-mediated lipid peroxidation in the differential cytotoxicity caused by two varieties of talc nanoparticles on A549 cells and lipid peroxidation inhibitory effect exerted by ascorbic acid." *Toxicology in Vitro* No. 24 (2010): 1139–1147

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American Thoracic Society. "Health Effects of Tremolite." *Medical Section of the American Lung Association* (1991).

Arellano-Orden, Elena, Auxiliadora Romero-Falcon, Jose Martin Juan, Manuel Ocana Jurado, Francisco Rodriguez-Panadero, and Ana Montes-Worboys. "Small Particle-Size Talc Is Associated with Poor Outcome and Increased Inflammation in Thoracoscopic Pleurodesis." *Respiration* 86 (2013): 201–9. https://doi.org/10.1159/000342042.

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Aust, Ann E., Philip M. Cook, and Ronald F. Dodson. "Morphological and Chemical Mechanisms of Elongated Mineral Particle Toxicities." *Journal of Toxicology and Environmental Health, Part B* 14, (2011): 40-75.

Baan, Robert, Kurt Straif, Yann Grosse, Béatrice Secretan, Fatiha El Ghissassi, and Vincent Cogliano. "Carcinogenicity of Carbon Black, Titanium Dioxide, and Talc." *The Lancet Oncology* 7, No. 4 (April 2006): 295–96.

Baandrup, Louise, Mette T. Faber, Jane Christensen, Allan Jensen, Klaus K. Andersen, Søren Friis, and Susanne K. Kjaer. "Nonsteroidal Anti-Inflammatory Drugs and Risk of Ovarian Cancer: Systematic Review and Meta-Analysis of Observational Studies." *Acta Obstet Gynecol Scand* 92, No. 3 (March 2013): 245–55.

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Chang, Stella, and Harvey A. Risch. "Perineal Talc Exposure and Risk of Ovarian Carcinoma." *Cancer* 79, No. 12 (June 15, 1997): 2396–2401.
Chen, L-M, et al. "Epithelial Carcinoma of the Ovary, Fallopian Tube, and Peritoneum: Epidemiology and Risk Factors - UpToDate," 2018. https://www.uptodate.com/contents/epithelial-carcinoma-of-the-ovary-fallopian-tube-and-peritoneum-epidemiology-and-risk-factors?search=Epithelial%20carcinoma%20of%20the%20ovary,%20fallopian%20tube,%20and%20peritoneum:%20Epidemiology%20and%20risk%20factors&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
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Therapeutics 30, (2009): 364-74.

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IMERYS 030347
IMERYS 031791
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Depositions

Deposition of Alice M. Blount Dated 4.13.2018
Deposition and Exhibits of Laura M. Plunkett Dated 1.11.2017-1.13.2017
Deposition of Dr. Thomas Dydek Dated 8.21.18
Deposition and Exhibits of John Hopkins Dated 8.16.18-8.17.18
Deposition and Exhibits of Julie Pier Dated 9.12.18-9.13-18
Deposition and Exhibits of Pat Downey Dated 8.7.18-8.8.18
Deposition of Robert Glenn Dated 10.18.18

Deposition and Exhibits of Donald Hicks Dated 6.28.18-6.29.8

Reports

Expert Report of Michael M. Crowley, PhD

Expert Report of William E. Longo, PhD and Mark W. Rigler PhD. Analysis of J&J Baby Powder & Valiant Shower to Shower Talc Products for Amphibole (Tremolite) Asbestos Expert Report. August 2, 2017.

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Expert Report (Brower v. J&J) of Dr. Thomas Dydek

Expert Report (Brower v. J&J) of Dr. Laura Plunkett

Supplmental Expert Report (Brower v. J&J) of Dr. Laura Plunkett

Exhibit 25

Migration of a Particulate Radioactive Tracer from the Vagina to the Peritoneal Cavity and Ovaries

P. F. VENTER, M. ITURRALDE

SUMMARY

In this report we describe a radionuclide procedure designed to evaluate the migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries, as well as the determination of the patency of the pathways between these two extremes of the female reproductive system.

^{99m}Tc-labelled human albumin microspheres (^{99m}Tc-HAM) were deposited in the posterior fornices of 24 patients a day before they were to undergo different gynaecological operations. During this period sequential images were obtained and after the operation radioactivity levels in the removed organs and tissues were counted with a scintillation detector.

In 14 out of 21 cases, the ovaries and fallopian tubes were counted separately from the uterus. Nine were positive (radioactivity levels were sufficiently high in the tubes and ovaries) and 5 were negative (no substantial radioactivity levels could be detected in either the tubes or the ovaries). The 5 negative results all occurred in patients with proved tubal damage as a result of previous infection.

All the results were either true positive or true negative, providing evidence of migration, or obstruction, of ^{99m}Tc-HAM from the vagina through the uterus and tubes to the peritoneal cavity and ovaries.

S. Afr. med. J., **55**, 917 (1979).

In the female, the peritoneal cavity is linked with the outside via the fallopian tubes, the uterus and the vagina, and there is evidence of migration of different substances in either direction. For example, malignant cells from ovarian carcinoma can be demonstrated in the posterior fornix of the vagina.[1] After menstruation the gonococcus can penetrate the cervix and gain access through the uterus and tubes to the peritoneal cavity and ovaries.[2] For pregnancy to occur, spermatozoa have to move up the uterus and the ova down the tube. Retrograde menstruation is also a well-known phenomenon. After insufflation, air and gases pass easily from the vagina into the peritoneal cavity up to the diaphragm. Radio-opaque contrast media are introduced with great ease through the uterus and tubes into the peritoneal cavity, and tubal patency is easily demonstrated during peritoneoscopy by injection of a dye through the cervix and into the tubes.[3]

Does this also hold for inert chemical substances? Will a chemical substance deposited in the vagina later appear in the peritoneal cavity? Such migration could well explain the aetiological role of chemical substances in certain gynaecological diseases. It has already been suggested that talcum powder is one of these potentially dangerous inert chemical products. Electron micrographic slides of removed human ovaries have shown asbestos particles resting on them, and there is evidence that these particles originated from talc used to dust condoms.[4]

To demonstrate the upward migration of chemical substances we made use of radionuclide imaging and counting techniques.

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Department of Nuclear Medicine, University of the Orange Free State and Academic Hospitals, Bloemfontein
M. ITURRALDE, M.D., D.M., *Professor and Head*

Date received: 22 November 1978.
Reprint requests to: Professor M. Iturralde, Dept of Nuclear Medicine, University of the Orange Free State, PO Box 339 (M. 27), Bloemfontein, 9300 RSA.

MATERIAL AND METHODS

The subjects of this study were 24 adult women, both Blacks and Whites, from the Academic Hospitals of the University of the Orange Free State in Bloemfontein. All had been admitted to hospital for elective gynaecological surgical operations (Table I). The radionuclide procedure was explained and the necessary consent obtained

TABLE I. SURGICAL INDICATION AND OPERATIVE PROCEDURE

Number of patients	Surgical indication	Operative procedure
4	Sterilization	Fimbriectomy
7	Ca. breast stage III	Bilateral salpingo-oöphorectomy
1	Ca. breast stage III	Hysterectomy and bilateral salpingo-oöphorectomy
2	Postmenopausal bleeding	Dilatation and curettage
2	Postmenopausal bleeding	Hysterectomy and bilateral salpingo-oöphorectomy
3	Menorrhagia	Dilatation and curettage
4	Menorrhagia	Hysterectomy and bilateral salpingo-oöphorectomy
1	Pelvic infection	Hysterectomy and bilateral salpingo-oöphorectomy

Procedure

The patient was placed in the supine position with the buttocks slightly elevated. The cervix and posterior fornix were exposed with a Cusco vaginal speculum and between 10 and 15 mCi of ^{99m}Tc-labelled human albumin microspheres (HAM) in a volume of less than 3 ml was

deposited in the posterior fornix. The patient was kept in this position for about 2 hours. The vulva was covered with a sanitary towel, and the legs were pressed together to prevent the radionuclide solution streaming from the vagina and thus lowering count levels.

In a few cases images were obtained, 4 and 24 hours after deposition of the radioactive tracer, with a Nuclear Chicago Pho/Gamma III scintillation camera (Figs 1 and 2). In most cases a count was performed on removed surgical specimens as a whole or separately on the uterus and adnexae, for 1 000 seconds in a 12,7-cm well scintillation detector. In one case a piece of the anterior peritoneum, fluid from the pouch of Douglas and blood were also included in the count, to determine the possibility of reabsorption into the bloodstream from the vaginal mucosa.

Radiation exposure to the patients was low owing to the short half-life of ^{99m}Tc (6 hours), and in most cases it was almost negligible since the target organs had been surgically removed.

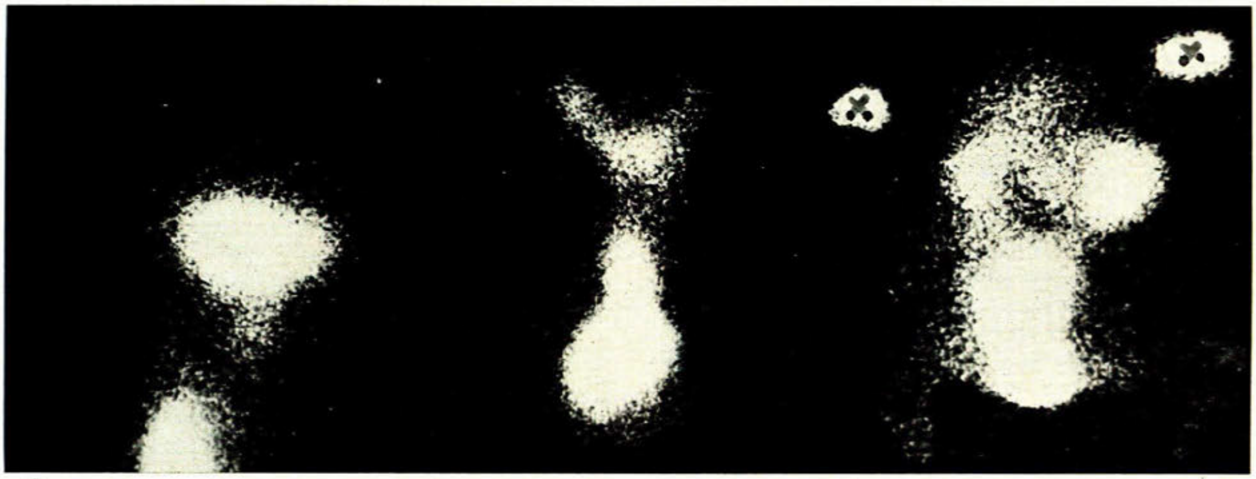

Fig. 1. Scintiphotographs showing positive ^{99m}Tc-HAM migration: A — from the vagina to the uterus (4 hours after deposition); B — in both tubes (6 hours after deposition); C — reaching the peritoneal cavity and ovaries 24 hours after deposition (markers in the anterior superior iliac spines).

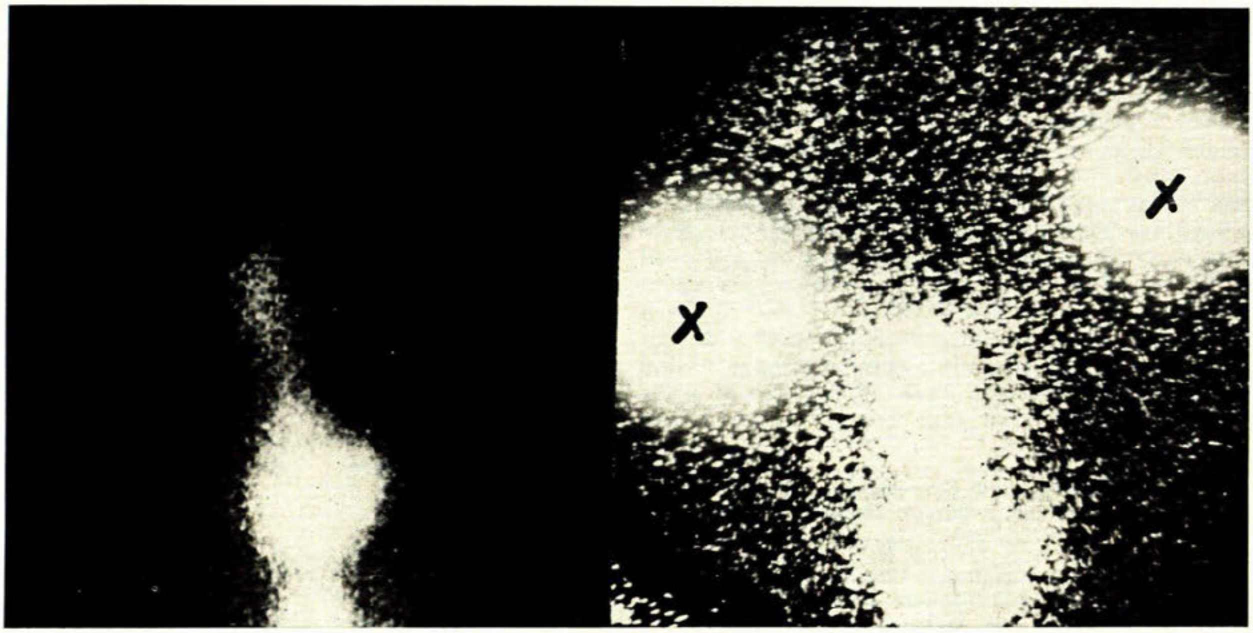

Fig. 2. Scintiphotographs showing negative ^{99m}Tc-HAM migration: A — in the left tube (4 hours after deposition); the right tube is patent; B — in both tubes; 24 hours after deposition radioactivity remains in the uterus (markers in the anterior superior iliac spines).

RESULTS

A total of 24 patients were examined. Because radionuclide material streamed away from the vagina in 3 patients, these cases were considered technically defective and were not included in the final analysis.

Of the remaining 21 cases 16 were positive, that is sufficiently high radioactivity levels were obtained as evidence of migration of the radioactive tracer to the uterus or the tubes and ovaries. The results were negative in 5 cases; in 2 of them the radioactive microspheres did not pass from the vagina to the uterus and in the other 3 there was no migration to the adnexae or fimbria. In the latter, it was impossible to determine radioactivity levels in the uterus because the latter was not removed.

TABLE II. SUMMARY OF RESULTS

Patient	Tissue examined	Radioactivity present (+) or absent (−)
1	Organ imaging fimbria	Uterus, adnexa, fimbria +
2	Organ imaging	Uterus and adnexa +
3	Organ imaging fimbria	Uterus, adnexa, fimbria +
4	Organ imaging adnexa	Uterus +, adnexa +
5	Uterus and adnexa	Uterus +, adnexa −
6	Endometrium	Endometrium −
7	Organ imaging endometrium	Uterus and endometrium +
8	Organ imaging endometrium	Uterus and endometrium −
9	Endometrium	Endometrium +
10	Uterus and adnexa	Uterus and adnexa +
11	Adnexa	Adnexa +
12	Uterus and adnexa	Uterus and adnexa +
13	Uterus and adnexa	Uterus, adnexa +
14	Endometrium	Endometrium +
15	Uterus and adnexa	Uterus +, adnexa −
16	Adnexa	Adnexa +
17	Adnexa	Adnexa +
18	Fimbria	Fimbria −
19	Uterus and adnexa	Uterus and adnexa +
20	Adnexa	Adnexa −
21	Adnexa	Adnexa −

In 14 out of 21 cases it was possible to measure radioactivity levels in the adnexa separately from the uterus. Nine of these showed marked radioactivity in the tubes and ovaries, while in 5 the radioactivity levels were not much higher than the background. In all 5 of these patients, severe tubal occlusion due to previous infection was confirmed by study of the removed specimens (Table II).

In 1 case, radioactivity levels in blood were not much higher than in the background, which indicated that radioactive tracer had not reached the adnexa through the blood supply owing to local reabsorption in the vaginal mucosa.

DISCUSSION

Evidence is available for migration of different substances in either direction within the female reproductive system between the peritoneal cavity and ovaries via the tubes, uterus and vagina, and the outside. Various living organisms actively follow this pathway in both directions. Gases, fluids, dyes and contrast media can easily be introduced from the vagina into the peritoneal cavity. If transit can take place so easily, it is probably the same for many chemical substances used for hygienic, cosmetic or medicinal purposes, many of which may have potential carcinogenic or irritating properties.

To prove this would be of great practical value, because migration of certain chemical substances could play an important aetiological role in gynaecological diseases and especially in carcinoma of the ovary.

We found the use of a particulate radioactive agent such as ^{99m}Tc-HAM with a size range of 30 - 50 μm to be a suitable and safe means of imaging and evaluating tubal patency and demonstrating the possibility of transit of particles from the vagina to the peritoneal cavity and ovaries.

Results obtained by this technique correlated with findings in the surgically removed specimens, thus demonstrating the accuracy of this radionuclide procedure.

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Exhibit 26

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

RULE 26 EXPERT REPORT OF JACK SIEMIATYCKI MSc, PhD

J Siemiatycki

Date: November 16, 2018

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Jack Siemiatycki MSc, PhD

EXPERT REPORT OF JACK SIEMIATYCKI MSc, PhD

On

TALCUM POWDER USE AND OVARIAN CANCER

Jack Siemiatycki, MSc, PhD, FCAHS

106 Columbia Avenue

Westmount, Quebec, Canada

November 16, 2018

TABLE OF CONTENTS

1. My mandate

I have been retained to assess the epidemiologic evidence regarding the **general causation** between perineal (or genital) use of talcum powder products and risk of ovarian cancer. The question is: "Can application of talcum powder products in the perineal region cause ovarian cancer?"

All of my opinions in this report are stated to a reasonable degree of scientific certainty.

2. My credentials, expertise and experience

I am a tenured Professor of epidemiology at the University of Montreal and an Adjunct Professor of epidemiology at McGill University in Montreal. I have received prestigious national research awards in Canada, such as National Health Scientist Salary Award, Medical Research Council Distinguished Scientist Award, Canada Research Chair in Environment and Cancer and, currently, I hold the Guzzo-Cancer Research Society Chair in Environment and Cancer. I am an elected fellow of the Canadian Academy of Health Sciences. I was awarded a lifetime achievement award by the Canadian Society for Epidemiology and Biostatistics, the premier professional organisation in our discipline.

Trained in statistics and in epidemiology, I have devoted most of my research career to investigating links between environmental, occupational and lifestyle factors and various types of cancer. My research has been both substantive – namely, looking at particular factors and their possible relationship to particular cancers - and methodological – namely, exploring how to evaluate and enhance the validity of epidemiologic research through various prisms: study design, data collection methods and statistical analysis. Of my approximately 250 research publications, about one quarter would be considered to have methodological focus.

I have held various leadership positions, including the elected presidency of the Canadian Society for Epidemiology and Biostatistics, and elected membership on the Board of the American College of Epidemiology. I have been invited to serve on over 160 Boards, Scientific Councils and Expert Panels for a host of governments, universities or research agencies. Examples include: Board of Directors of the Canadian National Cancer Institute, member of expert panel tasked with recommending priorities for action under the

Canadian Environmental Protection Act, member of external peer review panel of the Epidemiology branch of the US National Cancer Institute (NCI), member of two different expert advisory bodies to research projects at the NCI, consulted by President Clinton's Cancer panel, member of external peer review panel for the Helmholtz German national medical research agency, Chair of the Scientific Council of the largest prospective study of causes of cancer being conducted in France, and others of that nature.

I have been associate editor of the American Journal of Epidemiology and the International Journal of Environmental Health. In addition, I have served as reviewer for about 20 journals. I have served as a chair and as a member of grant review panels for major Canadian scientific funding agencies.

My research programme has been well funded by Canadian funding agencies for over 35 years. I have conducted research and published on the carcinogenicity of a large number of agents in the occupational environment (e.g. asbestos, silica, welding fumes) and in the general environment (e.g. smoke from wood stoves, urban air pollution) and lifestyle factors (e.g. smoking, alcohol, use of cell phones).

I have taught and supervised epidemiology students and many of my former trainees are now faculty members in universities around the world.

I have had a long association with the International Agency for Research on Cancer (IARC). IARC is the premier institution in the world for cancer epidemiology and for environment and cancer research. It has several mandates, including the organisation and compilation of standardised high quality data on cancer incidence around the world, the conduct of original research, and the evaluation of the carcinogenicity of different agents with which humans come into contact. The latter is achieved through a process that involves identifying chemical or physical agents for evaluation, convening specially selected international expert panels that are mandated to review all pertinent evidence on the topic and write a thorough review culminating in an evaluation of whether the agent(s) are human carcinogens. Since the inception of this program in 1971, there have been about 120 meetings held and approximately 1100 agents have been evaluated.

A particular point of pride for me is that over the years, research results from my team have been cited as part of the information base on 69 of the 1100 agents that have been evaluated, probably making my team the most cited epidemiology team in the history of the IARC Monograph program.

My association with IARC began when I did a post-doctoral fellowship there in 1977-79. Over the intervening years I have collaborated with scientists at IARC on various research projects. I was a member of the 18-member Scientific Council of IARC from 2006 to 2010 including two years as elected Chairman of the Council. The Scientific Council oversees all of the scientific activities at IARC; its members are named by the member states of IARC. I have been invited to sit on IARC Monograph international expert panels for 5 of the 60 panels convened in the past 25 years. One of the IARC Monograph panels of which I was a member was tasked with evaluating: "Carbon black, titanium dioxide and non-asbestiform talc." Out of the 16 invited experts who participated in the meeting as members of the Working Group, I was selected to chair the meeting.

Subsequent to the IARC meeting and the report of the meeting, a small subgroup of members of the IARC Working Group, of which I was a member, conducted and published a meta-analysis of the results of the studies that had been available to the IARC Working Group (Langseth, 2008)

Although I have not personally produced original data collection studies on the topic, I am well qualified to review the epidemiologic evidence. I have participated in two published reviews of the issue. The methodologic expertise and analytical skills required to critically review and evaluate such evidence is generic to the vast area of environmental epidemiology of cancer. I am routinely asked by journals and grant agencies to provide expert opinions on topics for which I have not produced original data collection studies, but that are within the purview of my expertise. The invitation by IARC to chair the meeting at which talc was evaluated is testimony to the fact that my competence and expertise in this matter are internationally recognized by peers. I do not claim expertise in various adjoining domains that inform this issue, including physiology, pathology, clinical oncology, experimental toxicology, geology and mineral chemistry. However, I do have the

expertise and skill to assimilate information that is provided by experts in these areas. I have previously submitted a report on my review of the evidence regarding talcum powder products and ovarian cancer in October 2016.

I have previously served as an expert witness for plaintiffs in one U.S. court case, and that was a talc litigation in Los Angeles in 2017. (Eva Echeverria, BC628228, Johnson and Johnson Talcum Powder Cases, CA JCCP No. 4872), and I testified that the genital use of talcum powder products can cause ovarian cancer.

I have served as an expert witness in two Canadian court cases, neither having to do with talc or hygiene powders or ovarian cancer. One case dealt with a class action lawsuit on behalf of a town in Canada adjoining a Canadian military base where there had allegedly been a spill of trichloroethylene that seeped into the water table of the town. The residents claimed that the contamination had caused cases of cancer. I was an expert for the defence, the Canadian government, and I testified in 2012. (Province of Quebec Superior Court file 200-06-000038-037).

The other case was a class action on behalf of Quebec residents who contracted cancer and had been smokers, claiming that the tobacco companies were responsible for their diseases. I was an expert for the plaintiffs and I testified in 2014. (Province of Quebec Superior Court file 500-06-000076-980).

In my work as an expert for legal cases, my time is billed at the rate of $450 per hour for research, report preparation, communications with counsel, participation in depositions, and testimony in court.

3. Overview of my methodology

The basis of my opinions derive from my education, training, experience, research and what is accepted within the community of leading scientists practicing in the field of epidemiology. My opinions are based on my review of the relevant materials, published in the scientific literature and/or produced in this case; including internal company documents, as well as relevant depositions, reports and testimony in the talcum powder product litigation. To reach my conclusions, I have employed the same scientific

methodology and rigor that I use in my research, in my publications and in the consulting and advising that I carry out on behalf of governments, public health agencies and research institutes. This includes a review of the relevant published literature, expert judgment to assess the quality and meaning of the various studies that were reviewed, and syntheses of the available evidence and any other pertinent medical and scientific evidence of which I am aware. The methods I used to derive and present my opinions are those used in general in the assessment of causal relations in medicine and public health, and more specifically in epidemiology. The methods are based on the experience and insight I have accumulated over 40 years of research, consulting, reviewing and student supervision, from discussions and interactions with leading epidemiologists, service on multiple IARC panels, and from reading evolving ideas in the scientific literature, including such seminal works as Bradford Hill's (Hill 1965) writings on assessing causality.

My opinions may be further supplemented and refined, subject to results that may come from further medical and scientific study and research and the continued review of additional information and discovery materials produced in this litigation.

4. The science of epidemiology

This section is designed to provide a non-specialist reader with information and definitions about epidemiology and biostatistics that are needed to understand the basis of my evaluation on talcum powder products and ovarian cancer. I do not present in this section the actual data and evidence regarding talcum powder products and ovarian cancer.

Epidemiology is the science of occurrence of diseases in human populations. It is concerned with the patterns of disease occurrence and also with identifying the factors that influence disease occurrence. These two sets of concerns are sometimes referred to respectively as descriptive epidemiology and analytic epidemiology. The first addresses such issues as the incidence of the disease in different geographic areas, in different time periods, or at different ages and sexes. The second addresses more focused questions on the specific environmental and/or lifestyle and/or genetic factors that might influence the incidence of disease.

The word "epidemiology" has the same etymologic roots as the word "epidemic", which signifies that, initially, epidemiology grew out of the study of epidemics. Such epidemics were often of a microbial origin (e.g. viruses, bacteria, parasites). But increasingly in the 19th and especially in the 20th century, it became clear that the etiology (i.e. causation) of chronic diseases such as cancer could also be elucidated by studying their patterns of occurrence.

While there were many studies carried out in the early to mid-20th century that we would now qualify as epidemiological in nature, the discipline of epidemiology and its methods started to become formalized in the 1950's and 1960's. There are now departments of epidemiology in most large universities that have health science research and teaching activities and there are many national and international societies of epidemiology.

Epidemiology is characterized by its mainly observational and non-experimental approaches. It is a discipline that is not primarily based in the laboratory; rather it is based in society. That is the source of its strength, and its weakness. Because it deals with people in the reality of their lives, it is the most pertinent approach to understanding the links between people's lifestyles and environments and their health and disease. However, because it is based in society, it by necessity confronts the extreme complexity of human lifestyles, environments and diseases. And because we cannot experiment with people's lives, we cannot control the conditions in which people are exposed. The methods of epidemiologic research are complex and differ from study to study. Statistical methods play an important role in trying to tease out the role of different variables and in determining whether the observed results may be attributable to chance, to bias or to real effects of putative risk factors. It is usually necessary to assemble evidence from several data-collection studies on a given topic before being able to draw inferences about causality.

4.1 Some basic measures and notions used in epidemiology

In this section I will review a number of concepts that need to be understood in order to properly understand my review of the evidence regarding talc powder and ovarian cancer. It is intended for readers who may not be expert in epidemiology. In this section I will not necessarily tie the concepts and definitions to the talc-ovarian cancer issue; that part will

be left for later. For now, I am simply introducing the non-epidemiologist reader to terminology and concepts with which she/he may not be very familiar.

Prevalence of disease. The prevalence of a disease refers to the proportion of a population who are living with the disease at any given point in time.

Incidence of disease. The incidence of a disease refers to the proportion of a population who are newly diagnosed with the disease during a certain period of time. The bridge between incidence rate and prevalence rate is the average duration of the disease, or how long people live with it before they are cured or pass away. In fact, while incidence and prevalence are foundational concepts in epidemiology, it is only incidence that figures prominently in the evaluation of carcinogenicity of talc.

Risk of disease. The risk of disease is a term that can refer to incidence or prevalence. The meaning should be clear from the context in which it is used. For studies of cancer, it almost always refers to incidence of disease. This is the way I will use the term in this report.

"Cause" of disease. A cause of a disease is any agent or characteristic (environmental, lifestyle or genetic) that increases the probability of getting the disease or it may simply advance or hasten the onset of the disease. It may act alone or it may act in concert with other factors over a lifetime to cause the disease. It may act immediately (e.g., cyanide as a cause of poisoning; lack of seat belt use as a cause of car accident mortality) or it may take many years for the effect to become manifest (e.g., lack of physical activity as a cause of obesity). There may be many different causes for the same disease. (See explanation of Multifactorial Etiology below.)

Risk factor. As defined in the Dictionary of Epidemiology (Last 2001), a risk factor is an aspect of personal behavior or life-style, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with a health-related condition. The term *risk factor* is used rather loosely and depending on the context it can refer to a factor that directly causes a disease or a factor that is a strong marker for the proximal cause of the disease. As it is often used, I will

mainly use the term "risk factor" as a synonym for the noun "cause" of the disease. (eg. "Smoking is a risk factor for lung cancer.")

Association. As defined in the Dictionary of Epidemiology (Last 2001), association refers to the degree of statistical dependence between two or more events or variables. Events are said to be associated when they occur more frequently together than one would expect by chance. Association does not necessarily imply a causal relationship.

Risk among unexposed (R_u) refers to the risk of disease among persons who are not (or were not) exposed to the agent under investigation. In this case, it would refer to the risk of getting ovarian cancer among women who *have never* used talc in the perineal region.

Risk among exposed (R_e) refers to the risk of disease among persons who are (or were) exposed to the agent under investigation. In this case, it would refer to the risk of getting ovarian cancer among women who *have* used talc in the perineal region.

Relative Risk: $RR = R_e/R_u$ = Risk among exposed/Risk among unexposed

When RR > 1.0, it indicates that exposure to the agent increases the risk of developing the disease. When RR < 1.0, it indicates that exposure to the agent prevents the disease.

When RR = 1.0, it indicates that the exposure to the agent has no bearing on the risk of getting the disease.

95% Confidence interval (95% CI). This refers to the precision of an estimate of a parameter. When we estimate the 95% CI for the RR, we are approximately saying that we are 95% certain that the true parameter underlying the study is within these limits. (The true interpretation is more subtle.)

Statistical significance of an association: Statistical significance is a measure of the departure of a set of data from some null hypothesis. Most commonly in epidemiology, the null hypothesis would state that there is no association between a factor and a disease. The null hypothesis can be operationalized in different ways, such as that the RR = 1.0, or that there is no trend between the degree of exposure and the RR. Once a study is conducted, the results can be compared with the expected results based on the null hypothesis, and the discrepancy from the null hypothesis is measurable with probabilities. This is done

either by computing a p-value or a confidence interval. If the p-value is very small or the confidence interval does not include the null value, then we say that an observed association between the putative risk factor and the disease is unlikely to be due to chance alone.

It is important to note that while statistical significance is a tool for assessing whether an observed association is attributable to chance alone, it is not a very effective tool for establishing the absence of an association. That is, the absence of statistical significance is not tantamount to proof of the absence of an association. The absence of statistical significance can be due to the true absence of an association, but it can also be due to the study not having sufficient statistical power or to bias or confounding in the research methods. Furthermore, it should be noted that the conventional dichotomization of results as "statistically significant" or not, based on a particular cutpoint on the p-value scale (eg. p = 0.05), is a gross simplification. The compatibility of the data with the null hypothesis of no association is in truth on a continuous scale and the dichotomization is arbitrary and potentially misleading, especially when the observed p-value is close to the arbitrary cutpoint.

In practice, epidemiologists have been moving away from using and reporting p-values and statistical significance, as it has become clear that the main contribution of an individual study is to provide an estimate of the relative risk and its range of plausible values, embodied in a confidence interval.

Cohort studies and case-control studies: Epidemiologic research projects can take many different forms. The two most common types of analytic epidemiologic studies are cohort studies and case-control studies. (Rothman, Greenland, & Lash 2008)

In a cohort study, it is typical to enrol a large number of subjects, determine which ones are or have been exposed to the factor of interest (e.g., talc) and follow them for some period of time to evaluate whether those who were exposed subsequently experienced different disease rates from those who were not exposed.

In a case-control study, by contrast, we start with people who have the disease under study (e.g. ovarian cancer) and a set of controls who do not have the disease, and we collect data

to determine whether the cases and the controls had different histories of exposure to the factor under study (e.g. talc).

It may be said that a cohort study proceeds from the cause to the effect, whereas a case-control study starts from the effect and backtracks to the cause. There are many variants on these basic designs. These descriptions of these types of study are somewhat simplified.

It is sometimes claimed that a prospective cohort design produces more valid and reliable RR estimates than a case-control study. But this is incorrect as a generalization. The validity and reliability are not determined by the overall architecture of the study, but rather by the specifics of the study, including how the study subjects were assembled, the nature of the variables under study (exposure, disease, confounders), exactly how the information was collected, the statistical power, and so on. There may be many reasons why a particular case-control study is more valid than a particular cohort study.

Relative Risk (RR) and Odds Ratio (OR). The cohort study design leads naturally to the estimation of risk of disease among exposed, and risk of disease among unexposed, and then to the ratio of those two, which is the RR. In case-control studies, because of the way the study samples are selected, it is impossible to estimate the risk of disease or the ratio of the two risks, R_e/R_u. However, under certain conditions which are well met in studies of cancer, it is possible to estimate an approximation of the RR. This is called the odds ratio, referred to as OR. In the rest of this report, I will consider evidence obtained from both cohort studies and case-control studies, and I will refer to the findings of these studies as RRs, even if technically speaking, the results from case-control studies are ORs.

Bias, confounding, effect modification. The aim in an epidemiologic investigation of a putative risk factor is to derive an accurate estimate of the RR between exposure to the agent and the disease at issue. Because the investigator does not control the conditions in which people live and are exposed to different agents and their willingness to participate in research, there are many potential sources of distortion in epidemiologic research. While there are many sources of distortion, they can be bundled into a few large families of sources of distortion.

Bias refers to a systematic distortion in study findings, resulting from the way the study was designed or the way the data are collected. Specific examples of types of bias will be discussed below as they pertain to talc and ovarian cancer.

Confounding is sometimes considered to be a type of bias, and sometimes it is considered a type of distortion on its own. This is merely a semantic distinction. Confounding refers to the situation where the association under study between factor F and disease D is distorted because there is a third factor X which happens to be correlated with F and which is a cause of disease D. For instance if we want to study the association between occupational exposure to talc in mines (factor F) and lung cancer (disease D), we need to be mindful of whether cigarette smoking (factor X) is more common in talc miners than in the rest of the population. Confounding differs from other types of bias in that it depends on relationships among different variables in the population, rather than characteristics of the study design and data collection.

Effect modification refers to the phenomenon whereby a given factor has a different effect in one sub-population than in another. If we study the association between that factor and the disease in the entire population without distinguishing the two sub-populations, we might end up with an estimate of the association that does not convey accurately the association in either sub-population. For instance, if it were the case that a certain genetic characteristic G increases the risk of pre-menopausal ovarian cancer but has no impact on post-menopausal ovarian cancer, then a study of the association between G and ovarian cancer that does not discriminate by menopausal status, would find an RR result somewhere between the null value among post-menopausal women and the true RR value among pre-menopausal women. Depending on the proportions of pre- and post-menopausal women in the sample, the overall RR might be so close to the null, that we might erroneously conclude that there is no association at all. In this example, it might actually be quite simple to detect the effect modification, since age is always recorded and menopausal status is usually recorded and investigators are sensitized to the possible effect modification of female cancers by hormonal status. Other potential effect modifiers may not be so easily available and they might not be on the radar screens of investigators. Effect modification can in some unusual circumstances completely wipe out a true causal

association (as when the agent causes cancer in some people but prevents cancer in others!). But generally, if there is a causal effect of the agent in one stratum of the population and no association in another stratum, and if we fail to stratify the population according to the effect modifier, it will have the effect of producing an overall RR that is lower than it truly is in the sensitive stratum and higher than it truly is in the insensitive stratum.

Effect modification is closely related to and sometimes synonymous with interaction or synergism.

Publication bias refers to the tendency for some evidence never to "see the light of day". Namely, when results are "negative" or "null", it may be that investigators never bother to submit them for publication, or alternatively that editors refuse to publish them. This happens, most likely, when the hypothesis under study is not particularly topical or controversial, and when the study is small.

In this section I have briefly outlined some potential sources of distortion of a typical epidemiologic study. I have done this in a high-level generic way. Below, after presenting results of my review of pertinent literature on powders and ovarian cancer I will return to commenting on the possible impact of such distortions in this body of literature.

Exposure variable and exposure metric

An ***exposure variable*** can be anything that can influence the occurrence or outcome of disease. The term is used for such disparate entities as external components of what we eat, drink, breathe, hear or see and microbiological organisms, chemicals or forms of radiation.

Depending on the nature of the variable, information on an exposure variable can often be ascertained from epidemiologic study participants by questioning them. This is the case for variables like cigarette smoking or use of talc powders. For some variables, like exposure to a virus or to specific air pollutants or occupational chemicals, it is usually necessary to invoke more intensive data collection methods to ascertain exposure.

An ***exposure metric*** signifies a way of defining a variable for statistical analysis. The simplest metric is a binary variable: exposed or unexposed. For most exposure variables, like exposure to talc powder, there can be a very wide range of degree of exposure. And it is pertinent to create more nuanced exposure metrics that take into account the degree of exposure that different people have experienced, metrics such as duration of exposure, intensity or frequency of exposure and even cumulative measures of exposure over long periods of time.

Measurement error. Whenever we are measuring a variable in an epidemiologic study, be it smoking, or weight, or socio-economic status, or blood pressure, or any other variable, it is virtually inevitable that there will be some degree of error in the measurement. There are ways of collecting data that make them more or less likely to involve error, but it is almost impossible to ensure that variables are measured with perfect validity and precision. Even such a variable as the diagnosis of ovarian cancer is subject to differences of opinion among pathologists and oncologists and the presence or absence and the histologic type of tumour is not a guaranteed 100% perfect diagnosis. The ascertainment of the lifetime history of talc exposure by means of an interview with a woman in middle age or later in life is certainly susceptible to the caprices of memory and the way the questions are formulated may influence the validity of respondents' reports of lifetime exposure patterns. It is likely that habits that were performed regularly are more reliably recalled than activities that were sporadic or that only occurred many decades earlier. Similar issues arise for all other variables collected in such studies. We refer to measurement error as random (or non-differential) if the degree of measurement error does not differ between cases and controls in case-control studies or between exposed and unexposed in cohort studies. As a general rule of thumb, it can be asserted that random (or non-differential) measurement error has a predictable distorting effect on the RR. Namely, while there are some rather obscure exceptions, non-differential measurement error tends to attenuate the RR towards the null value of 1.0, and the more measurement error, the greater the attenuation. A full explanation for why this is so is quite technical and can be found in advanced epidemiology textbooks, such as Rothman, Greenland and Lash 2008. A very simple explanation is that the presence of measurement error in assigning exposed vs

unexposed status leads to dilution of both the exposed group and the unexposed group. That is, the ostensible exposed group (i.e. the folks who will be labelled as exposed based on the study data collection) will contain some folks who are truly unexposed and the ostensible unexposed group will contain some folks who are truly exposed. If there really is a difference in risk between the true exposed group and the true unexposed group, this difference will be watered down by the inadvertent inclusion in each group of folks who are really in the opposite group. An analogy is the cross-contamination of two cans of paint. Suppose we have a can of pure white paint and a can of pure red paint. Suppose we have a way of quantifying the difference in color tone between the two paints. Then suppose we take some spoonfuls from the red can and pour them into the white can, and likewise take a few spoonfuls of the white paint and pour them into the red can. Now the color contrast between the two cans has been attenuated. The color contrast in this example is like the relative risk in an epidemiological study which has been attenuated because the exposed and unexposed groups have been cross-contaminated.

Dose-response. It is important not only to assess whether there is an association between a variable and a disease when the variable is defined in a binary (exposed vs unexposed) way, but also when the variable is defined in a quantitative or semi-quantitative way. When we analyse the risk as a function of the degree or duration or intensity of exposure, we refer to this as a dose-response (or exposure-response) analysis. The example of the smoking and lung cancer is instructive about the value of different metrics, though it cannot be assumed that all risk factors act the same way. Studies using the binary metric for smoking (smoker/non-smoker) have been very consistent and persuasive in demonstrating an association between smoking and lung cancer. Further, when data are collected and analysed regarding the degree of smoking, it becomes clear that there is a monotonic dose-response relationship. That is, the more smoking, the higher the risk. And the quantitative metric that manifests the strongest association with lung cancer is the cumulative amount smoked over the lifetime. This is perfectly logical. Since the cumulative exposure metric embodies information on duration and on intensity, it can hardly be less predictive of risk than either of the dimensions alone.

We cannot assume that there is a universal form of a dose-response relationship for every true causal relationship. Most commonly, in toxicology and epidemiology, the relationship between exposure and risk is monotonic; that is, as one increases, so does the other. This can include linear relationships (i.e. where a straight line on a graph describes the relationship) or exponential or many other curvilinear forms. It is also possible that there may be a threshold effect (the risk only becomes apparent after a certain level of effective exposure) or some other non-standard relationship.

Both the qualitative metrics (ever/never) and quantitative metrics (a lot of use compared with a little use) are valid and useful metrics.

Sample size refers to the number of participants in the study. As a generalization, large studies produce more statistically stable and precise estimates than small studies. In fact the stability of estimates or precision of estimates is not a simple function of the number of participants, or subjects, in a study. The precision of estimates depends, among other things, on the type of epidemiologic design.

In a case-control study the main determinants are the numbers of cases and controls and the prevalence of exposure in the two groups; in a cohort study the main determinants are the numbers of participants, prevalence of exposure, and the incidence of the disease of interest over the period of follow-up in the exposed and unexposed groups.

There is sometimes confusion about the notion of sample size when we compare cohort studies with case-control studies. The operational aspect of an epidemiologic study of cancer that most influences the precision of an estimate of RR is not the total number of participants; rather, it is the smaller number between the number of exposed cases of disease and the number of unexposed cases. In a typical prospective cohort study, one might need to enroll 100,000 participants in order to end up with a certain number of cases (say, 500 cases) of the disease of interest (e.g. ovarian cancer). In a case-control design we might only need to enroll around 500 cases and 1500 controls to achieve the same statistical power as would be achieved by a cohort study of 100,000. The formal justification for this assertion is quite mathematical, and has to do with the fact that a sample of a population can give very accurate estimates of the characteristics of an entire

population. Thus, the simple comparison of 100,000 participants in a cohort study and 2,000 participants in a case-control study is in no way a valid marker for the relative statistical power of the two hypothetical studies. There are admittedly other advantages and disadvantages of the cohort vs the case-control design, and reviewers should consider the various aspects before deciding on the relative weight to give to the results of the different studies. But it is definitely not appropriate to merely compare the numbers of participants as an indicator of study validity.

While precision is based on multiple factors and different ones in case-control and cohort studies, there is a parameter which embodies the different factors quite well, and which is common to both case-control and cohort studies, namely, the number of exposed cases. For this reason, in laying out the various study results below, in addition to the relative risk estimates and their confidence intervals, I will show the numbers of exposed cases.

While it may affect the precision of estimates of RR, the size of the study does not in itself systematically affect the estimates of RR. That is, it is not the case that small studies produce systematically exaggerated RR estimates or systematically low RR estimates. However small studies can produce more wildly divergent RR estimates than large ones, in either direction, towards the null or away from the null.

Meta-analysis and pooled analysis: There are two distinct ways that evidence from multiple studies can be combined to derive a new overall statistical summary or synthesis of those studies, a meta-analysis and a pooled analysis. A meta-analysis uses the published results from each study and averages those results using some optimal weighting procedures. In order to implement a meta-analysis it is necessary to find all relevant studies on a topic that have published results in a fairly standardized way. The statistical algorithms typically used to average the results from different studies also provide statistics that evaluate how heterogeneous are the results from the different studies. The interpretation of such heterogeneity statistics is not straightforward. If the results from different studies are homogeneous, it adds to the confidence in the meta-estimate. If they are heterogeneous, it may indicate that the association is really different in different populations, or that there are some methodological characteristics of the different studies

that have influenced the results in different ways. Unless a significant methodological flaw can be identified that has caused the heterogeneity, the best overall estimate remains the meta-estimate.

A pooled analysis is one in which the investigator gets access not only to the published results from different studies, but rather to the individual data of every person in the studies. The latter is harder to achieve because it requires high buy-in and input from the investigators of the original studies; a meta-analysis is much easier to organise. Because a pooled analysis allows for standardization in the definition of variables and statistical models, it can be a more powerful means of summarizing data than the original studies themselves.

Multifactorial etiology of disease. Chronic diseases such as cancer are multifactorial in two distinct ways. On the one hand, each case of disease results from the unfortunate conjuncture of a combination of factors (these might include for example, genetic predisposition, diet, environmental pollutant, occupational exposure, medical intervention, viral infection, lifestyle habits, etc.) which combine over a lifetime to initiate and promote development of the disease. In this sense, each of the factors that are part of the combination for that person was a necessary contributor to the disease process, although it was not sufficient on its own to provoke the disease. Despite the fact that none of the factors were sufficient to produce the disease on their own, each of the contributory factors may be considered to be a cause of the disease. The disease would not have arisen if any of the contributory factors had been absent. This is one meaning of the multifactorial etiology of disease.

The second meaning is that the combination of factors that induce cancer in one person may not be the same as the combination that induces cancer in another person. Indeed, at the population level, there may be many combinations of causal factors for the same disease. Some factors may be common to different combinations. For example, it may be that in one case of lung cancer, the combination of factors included genetics, exposure to air pollution, exposure to radon in the home, and smoking; while in another person, the

combination of factors included genetics, insufficient dietary consumption of anti-oxidants like carotene, exposure to asbestos, and smoking.

Some characteristics of carcinogens and epidemiologic research on cancer: The following characteristics of most known carcinogens provide a framework for some of the thinking behind the design and interpretation of epidemiologic studies of cancer.

- There is typically a long induction period between exposure to a carcinogen and appearance of the disease. Thus, if a study has not allowed for a sufficient passage of time between the exposure and the disease, the result may report that there is no risk, where in fact there is a risk, but insufficient time has elapsed to make the risk visible.
- There is variability in the carcinogenic potency of different carcinogenic agents; some induce much greater relative risks than others.
- For any given carcinogen, the degree of risk due to exposure generally increases as the exposure level increases, but the shape of the dose-response curve may differ from one carcinogen to another.
- Most known human carcinogens were first discovered as such either by means of astute observation of a clinician noticing a cluster of cases among people who shared a common characteristic (such as working in a particular workplace) or by means of epidemiological research. In most cases, there was no known mechanism to explain the association at the time. Where the mechanisms have been elucidated, they were usually discovered subsequent to the epidemiologic demonstration of a causal relationship. (Siemiatycki 2014)

4.2 Bradford Hill "guidelines"

Because of the complexities of epidemiologic research, there has been some concern with how epidemiologic evidence should be used to draw causal inferences. Various authors have written about the types of information that might be considered in assessing whether a body of evidence demonstrates a causal relationship. A set of guidelines, developed in the context of the Surgeon-General's Report on Smoking and Health (1964) and authored by

Bradford Hill in 1965, has achieved a wide consensus in the epidemiologic community as a pedagogical guide. Hill himself referred to these guidelines as "aspects" or "features" or "characteristics" of an association, and warned against treating them as "hard-and-fast rules of evidence that must be obeyed". (Hill, 1965) He deliberately avoided referring to them as "criteria."

Since Hill wrote those thoughts at the beginning of the era of modern epidemiology, without the benefit of decades of practical experience in the way those thoughts were taken up, and how they applied to issues other than smoking and cancer, it is understandable that the practice of evaluation of causality has evolved. A first observation, often overlooked, is that Hill took as a starting point for his writings that chance had been considered as an explanation for the smoking-cancer association and determined to be unlikely. In the historic context of 1964-1965 and the debates around smoking and cancer, this was a reasonable assumption to make, but for any other putative associations, this must be considered. Over the years, respected authors have paraphrased and updated these aspects in various ways, and this will undoubtedly continue. For instance, leading textbooks of epidemiology as well as the Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) all have different formulations of Hill's guidelines.

In the light of 50 years of practical experience after these guidelines were written, and based on my practical experience of evaluating causality in many forums and on many topics, I would paraphrase (and modernize) Hill's guidelines as follows:

<u>Strength of the association:</u> This can be measured by different parameters, but for cancer studies it is usually measured by the magnitude of the relative risk or odds ratio.

<u>Statistical significance of the association:</u> While this guideline was not explicitly listed by Hill, it is nonetheless in practice an implicit and distinct consideration in assessing causality. If the estimated RR is quite high, indicating a strong association, but is based on a very small study with low precision, this might be solely due to statistical variability. (For instance, when we flip a balanced coin 10 times, we do not always end up with 5 heads and 5 tails. Sometimes, by chance, we may end up with 6 heads and 4 tails. Does this prove that the coin was not balanced?) Evaluating the role of statistical chance as a possible

explanation of the observed association is important. As explained above, the absence of statistical significance is not strong evidence of an absence of a real relationship.

Dose-response relation: If the relative risk increases when the exposure increases, it enhances the likelihood that the observed association is really causal. There are some counter-examples however where the effect is only observed after a threshold of exposure has been crossed. There are various ways to assess whether there is a dose-response relation. Hill pointed out that the main challenge is to establish reliable and measurable quantification of exposure. In studies of lifestyle habits like use of talcum powder products, the most common way is to estimate the RR in increasing categories of exposure metrics such as duration (years) of usage, or intensity of usage (frequency per day or per week or per month), or cumulative amount of usage (a combination of duration and frequency).

Absence of bias: There are many forms of bias that can infiltrate an epidemiologic study. It enhances the likelihood of a true causal association if we can confidently exclude all the plausible sources of bias explanations for the observed findings. This guideline can also be considered as a component of a guideline to consider other possible explanations for the association.

Temporality: It is clear that the exposure should precede the outcome (i.e. the disease). To ascertain whether the cancer was a result of the exposure or the exposure occurred after the cancer onset seems like a simple thing, but sometimes it can be difficult to ascertain with certainty.

Cessation of exposure: It would add to the credibility of the association if it had been demonstrated that subjects who cease exposure to the agent experience reduced risks of disease compared with those who continue to be exposed. In practice this is an extremely difficult characteristic to demonstrate, partly because of the difficulty or even ethical impossibility of changing people's habits for scientific experimentation purposes. But occasionally there may be a "natural experiment" wherein large numbers of people cease their exposure and the effects can subsequently be measured in an epidemiologic fashion.

Specificity of the association: It was believed that individual risk factors have specific pathological effects, and Hill posited that if we observe that a given agent is associated with

many different pathologies, it increases the likelihood that these are somehow spurious observations, resting on some type of bias in the studies of that agent. In reality, this Hill characteristic has fallen out of usage in the intervening years with the demonstration that some agents can indeed provoke multiple different pathologies. Examples include cigarette smoking, ionizing radiation and asbestos fibers.

Consistency of findings between studies (or replication of findings): Because epidemiologic research is susceptible to errors from random variability and from different kinds of study biases, before accepting the apparent association as a generalized phenomenon, it is important to see that similar results are replicated in different studies. When these different studies also encompass different study populations in different communities, it enhances the generalizability of the inferences. Generally speaking, the observation of consistent results in different studies adds to the credibility of an inference that there really is a causal relationship.

Coherence with other types of evidence: In the case of tobacco and cancer, it was seen that the historic trend in lung cancer mortality rates in the US and UK followed quite closely the national trends in consumption of tobacco, with a 20 year lag. This was interpreted by Hill as corroboration of the results observed in case-control and cohort studies. Epidemiologic evidence of coherence could conceivably take many forms, and the opportunity to assess coherence is something that is specific to the factor under investigation. Assessment of coherence with historic mortality trends would only be possible in the case of a factor whose exposure in the population changed quite dramatically over time in a way that can be documented, and for which the attributable fraction of the disease due to that factor is very high. This was the "perfect storm" of circumstances that allowed for an assessment of the tobacco-lung cancer association by means of time trend correlations.

Analogy: Hill reasoned that if a factor is somehow similar to another factor that has already been shown to be a risk factor for the disease, then it increases the plausibility of a similar impact due to that putative factor. This is such a vague guideline, with no clear implementation suggestions, that it is not often referred to and rarely implemented.

Biologic plausibility: This guideline can encompass many dimensions of information, including physiology (can the agent or its metabolites reach the organ?), animal carcinogenesis (does the agent produce tumours in experimental animals?), cell studies that reveal mechanistic data, and other biologic information on the toxicology of the agent.

Implementing Hill's guidelines: As Hill himself insisted, sophisticated users of these guidelines do not use them as a formal checklist. He summarized his views as follows:

> « What I do not believe … is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect? »

The authors of the Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) clearly stated that Hill's guidelines are not formal criteria, but rather are more in the nature of a memory aid to help us review the evidence about any given causal association. They stated it this way: "There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines."

I have served on many panels to review evidence of causality on one topic or another, including on several IARC Monograph panels that reviewed evidence of carcinogenicity. The IARC process, like the others I have participated in, does not use the Hill guidelines in any rigid formal way. The ideas embodied in Hill's guidelines permeate our thinking about how to evaluate causality, but the operationalization of these guidelines is specific to the problem and to the expert making these determinations. Thus any suggestion that Hill's "aspects" or "features" or "characteristics" of an association should be used as a formal checklist of criteria is simplistic and wrong. To do so would contradict the opinions of experienced epidemiologists, the Manual on Scientific Evidence, and Bradford Hill himself.

In this section, I have laid out and explained the Bradford Hill guidelines in a generic way. Below, in section 8, I will consider how these apply in the context of the talcum powder – ovarian cancer issue.

5. Epidemiologic evidence regarding talc and ovarian cancer

Following some reports in the early 1980's that raised questions about a possible link between use of cosmetic talc powder by women and the risk of ovarian cancer, there were several epidemiologic studies on the topic. By the early 2000's the issue was garnering some attention in the scientific community. The International Agency for Research on Cancer, the premier agency for evaluation of carcinogens, decided to conduct a review of the issue in 2006. Following that review, there have been further studies conducted on the topic.

In the context of a legal action, my mandate is to review all relevant scientific evidence available to date, in order to provide the court with my opinion regarding the link between talc powder exposure and ovarian cancer. The methodology I employed is the same one I have used in my career as an internationally recognized researcher.

5.1 IARC review and evaluation of talcum powder products

As mentioned above in Section 2, the International Agency for Research on Cancer (IARC) is the premier institution in the world for cancer epidemiology and for environment and cancer research. One of its mandates is the evaluation of the carcinogenicity of different agents with which humans come into contact, and this mandate is carried out by the Monograph Programme of IARC. This is achieved through a process that involves identifying chemical or physical agents for evaluation, convening specially selected international expert panels that are mandated to review all pertinent evidence on the topic and write a thorough review culminating in an evaluation of whether the agent(s) are human carcinogens.

In February 2006, there was such an IARC Monograph meeting to evaluate some agents, including talc. The IARC Working Group comprised 16 highly respected and recognized scientists from around the world; I was asked to Chair the Working Group. We reviewed all

the evidence that was available up to that point in time. This certainly included epidemiologic evidence, but it also included evidence from experimental toxicology, physiology, molecular biology and other domains. The IARC Monograph programme has a formal system for classifying agents. The Working Group must classify an agent into one of the following categories:

1	Carcinogen
2A	Probable carcinogen
2B	Possible carcinogen
3	Not classifiable
4	Not carcinogen

After reviewing the evidence, the panel concluded that talc was a "possible carcinogen", based primarily on evidence regarding the association between dusting powders and ovarian cancer. Here is the definition of this category from the IARC Monograph:

> "Group 2B: The agent is possibly carcinogenic to humans.
>
> This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals."

This 2B categorization was based on the panel's decision that there was "limited evidence of carcinogenicity in humans", which is in turn defined by IARC as follows:

> "Limited evidence of carcinogenicity in humans: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."

Subsequent to the completion of the IARC Monograph on talc, a subgroup of the epidemiologists who were on the IARC Working Group, including myself, reviewed the evidence again, but with a view to producing a meta-analysis of the results from the most informative studies conducted to that time. This resulted in the paper by Langseth et al. (2008). This paper was not an IARC publication.

5.2 Information consulted for the present review

In preparation for formulating my current opinions on this topic I assessed, researched, reviewed and consulted a large number of documents, including, but not limited to: all original epidemiological studies published on this topic, all meta-analyses and opinion pieces, experimental toxicology, molecular biology, mechanistic studies, and the IARC Monograph on talc which reviewed all informative studies that had been published before 2006. I was given access to and also reviewed the various expert reports and depositions that have been submitted in various talc cases, either on behalf of the Plaintiff or Defendant, and various internal company documents obtained in discovery.

I systematically reviewed the lists of references of all relevant studies referenced in the IARC report as well as in various meta-analyses and in all recent articles on the topic to identify yet more relevant publications on talc and cancer.

Because some studies have been published in multiple papers and because some papers have included reports on multiple studies, there is not a one-to-one relationship between studies and published papers.

Additionally, I considered evidence regarding the toxicology of talc by reviewing the toxicology evaluation conducted by the IARC Working Group, the summary of talc's putative toxicology referenced in various scientific publications, and the expert reports of various scientific/medical experts in this case.

The central focus of my review is on the epidemiologic evidence.

A complete listing of the documents I consulted, as well as references cited explicitly in this report, is provided in the Bibliography. The Bibliography is in two Parts; Part A comprises all the publications and reports that can be found in publicly available scientific literature. Part B comprises company documents or documents from reports or testimonies of experts.

5.3 My methodology for this review

Table 1 lists the steps I undertook to accomplish my mandate.

5.3.1 Selecting studies for review

To aid in the present assessment of whether or not there is a causal relationship between talcum powder exposure and ovarian cancer, I carried out an up-to-date review of the scientific literature, primarily the epidemiologic literature, concerning the association between use of talc powder and risk of ovarian cancer. This involved meta-analyses to estimate the effect of having ever used perineal powdering, and an assessment of evidence regarding dose-response.

The first task was to find the relevant publications and to set out the distinct pieces of epidemiologic evidence, namely the results of different studies. Based on a number of reviews on the topic of talc and ovarian cancer, including the IARC report, I systematically went through the reference lists to identify all publications that seemed to contain results on the topic. I further conducted a Pubmed search and this did not produce any new informative publications that had not already been identified. In preparation of the meta-analysis, I eliminated from consideration papers that were outside the bounds of what a meta-analysis should contain (i.e. eliminate review articles, commentaries, meta-analyses, and articles that do not really pertain to the issue of perineal talc and ovarian cancer). From the 40 publications that remained, namely those that contained original results on the association between powdering and ovarian cancer, I extracted all results showing RRs between talc powdering and ovarian cancer, and I had these results put into a Filemaker database. This was a value-free exercise. I made no judgement at that stage about relevance or quality of the study or the published results. It was only an attempt to lay out in one "place" the whole of the evidence and to prepare for subsequent analyses. There were over 730 results in this database. On average each publication contained about 18 different RR results of various aspects of talc powder exposure and various types of ovarian cancer. Some contained fewer and some contained many more. (For instance, one study publication contained 180 results, with varying types of ovarian cancer and varying definitions of exposure to powdering.)

In deciding which results to include in a meta-analysis I had to respect the following principles:

- The results have to pertain to the issue of risk of ovarian cancer in relation to use of talc-based powders.
- Where there are sufficient numbers of results to support meta-analyses, there can be meta-analyses for different types of ovarian cancer, and for different routes of exposure to talc-powders.
- In each meta-analysis, each study should only provide one result, so as to avoid double-counting evidence.
- The decision about inclusion of a study should in no way be influenced by whether or not a particular study demonstrated high risks or low risks.

While these seem like simple principles to respect, there were complicating features of the scientific literature:

- Some studies were reported in multiple publications, sometimes the same study subjects were analysed and reported in different ways and sometimes different subsets of the study population were included in different publications. Sometimes the authors fail to clearly enunciate how the data used in one of their papers overlaps with data used in another of their papers from the same study.
- Different studies used different questions about powder use in their questionnaires, and sometimes the same study reported results by different ways of asking about or defining exposure.
- A given study may have presented one result or many results, each addressing a different definition of the talc exposure variable and different way of grouping the ovarian cancer cases.
- Different studies dealt differently with the histologic sub-types of ovarian cancer, sometimes grouping them all, or sometimes separating them, or sometimes reporting both grouped and separate results for different sub-types.

- Different studies used different metrics for analysing powder exposure and estimating its corresponding RR.
- Different studies dealt differently with the challenge of adjusting powder-related risks for possible confounding by other factors.

Decisions had to be made regarding which types of exposure to consider, which types of ovarian cancer to consider, which metrics of exposure to consider and which studies and publications to consider. It is necessary to be rigorous in making such decisions ahead of time, rather than "cherry-picking" results from different studies that appear to support one theory or another.

Appendix Table A1 provides a list of those 40 publicly available publications that have included some original results that might pertain to the association between powdering and ovarian cancer. **Appendix Table A1** shows which publications were included and which papers were excluded from my meta-analyses. For each of the 14 excluded papers, the table also shows the reason. Some papers were excluded because the results did not pertain to ovarian cancer and powdering in the perineal region. Some papers were excluded because the results presented therein were subsumed by a subsequent publication by the same research team or as part of a pooled analysis of multiple studies. Notwithstanding my intention to identify all unique studies and to extract a best "bottom line" result from each study, the nature of the studies and how they were analysed and reported led to many judgement calls. It must be acknowledged that there can be differences of opinion among equally competent and equally well-motivated scientists in how to choose among the different publications and the different results within publications.

Fortuitously, and unbeknownst to me at the time, two other sets of investigators (Berge et al 2018; Penninkilampi et al 2018) carried out separate meta-analyses on this topic at about the same time as I was carrying out mine, and this gives an opportunity to do some cross-comparison of different reviews and meta-analyses. I will comment on these after presenting the results of my meta-analyses.

5.3.2 What were women exposed to in body powders?

Talc has been the main ingredient of body powders used by women over the past century. "Talc particles are normally plate-like. When viewed under the microscope in bulk samples or on air filters, they may appear to be fibers ... Talc may also form as true mineral fibers that are asbestiform; asbestiform describes the pattern of growth of a mineral that is referred to as a 'habit'. Asbestiform talc fibers are very long and thin."(IARC 2010) The structure of platy talc is characterized by a hexagonal sheet arrangement of silicon-oxygen tetrahedral groups in a common plane which creates a double-sheeted structure. These sheets are easily separated which accounts for the "silky" or "smooth" feel of talcum powder products (IARC, 2010). As a mined mineral, the precise chemical and physical characteristics of talc are in part determined by the particular geological formations from which it is extracted. The local conditions can also produce "impurities" in the extracted talc including asbestos, quartz and various metals. It is claimed that cosmetic talcum powder products normally contain >98% talc (Zazenski *et al.*, 1995) but the purity may have been lower in the past. (IARC 2010) When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products and all constituent elements contained in those products.

Asbestos is a commercial term that comprises six minerals that occur in the asbestiform habit: actinolite, anthophyllite, chrysotile, grunerite, riebeckite and tremolite. Similarly to talc, these six minerals can occur in a non-asbestiform habit. Some types of asbestos are found in the same geological formations as talc.(IARC 2010)

By the 1970's it was reported that asbestos fibers were found in commercial talcum powder (Cralley 1968; Rohl 1976), though there was some doubt expressed regarding the quantification of the exposure and the ability to discriminate between asbestiform and non-asbestiform talc. (Krause 1977; IARC 2010) The talc industry was constrained to remove asbestos from talcum powder products. Representatives of the industry have claimed that talcum powders were free of asbestos fibers since the 1980's (Hopkins 2018; Pier 2018), but this assertion has increasingly come under doubt as number of labs have

reported finding asbestos fibers in talcum powder products. (Blount 1991; Paoletti 1984; Gordon 2014; Longo et al 2017; Longo et al 2018; Blount deposition 2018; Pier deposition 2018) These various studies that have reported finding asbestos in historic talcum powder samples have been challenged by other reports that failed to find meaningful amounts of asbestos in historic talcum powder samples. (CIR 2013; Anderson 2017) These various findings and opinions are somewhat complicated by the fact that both talc and asbestos have varied chemical and physical characteristics and various methods can be used to measure them.

What is clear is that asbestos, and all forms thereof, has been evaluated to be carcinogenic. It has long been recognized that inhalation of asbestos carries with it a risk of lung cancer and of mesothelioma, a cancer of the lining of the lungs, as well as larynx cancer. What has only recently been recognized is that women who are exposed to asbestos experience an excess risk of ovarian cancer. (Straif 2009; IARC 2012) This conclusion was based on five studies; a subsequent meta-analysis reported that the RR of ovarian cancer among asbestos-exposed women was a highly statistically significant 1.77 (1.37-2.28).(Camargo 2011) The route of exposure that generates risk of ovarian cancer among women exposed to asbestos is not clear, but inhalation and migration of asbestos particles to the ovaries has been proposed as a credible biologically plausible mechanism. (Miserocchi 2008)

Among the metals detected in talcum powder products are some which are recognized carcinogens, namely nickel and chromium. It is not known how widespread was the "contamination" of talcum powder products by these metals and how high were the concentrations in the entire commercial production of talcum powder products of the past several decades, and how these exposures measure up to exposures that may cause cancer. However, evidence that asbestos and some other known carcinogens have been detected in some commercial cosmetic talcum powder products and credible mechanisms that such particles can translocate to the ovaries is an important consideration in deriving an opinion on biological plausibility, and I will consider it below in my section on biological plausibility of a causal link between talcum powder products and ovarian cancer.

Alternative formulations of baby powder include cornstarch formulations, which have become available in the past 30 years. It was possible for women to purchase and use cornstarch products or talcum powder products. Most epidemiological studies have not tried to ascertain whether the women in their studies used talc-based or cornstarch-based formulations and many women may have been unaware of the composition of the powders they used at different times. It is impossible to ascertain with certainty from most of the publications whether the reported epidemiologic results pertain to talc-based powders or cornstarch-based powders or both. Those studies that did report results for cornstarch had few women self-reporting use of cornstarch and the risk estimates were rather imprecise and unstable. For those studies that did report separately the findings for talc-based and cornstarch-based formulations, I used the results for talc-based powders. For those that did not make such distinction, I used the results combining all types of powders as reported. If it turns out that there is an increased risk associated with talc but not with cornstarch, the inability to discriminate the two in statistical analyses would have the effect of diluting the estimates of risk due to talc. That is, the RR estimates would be attenuated.

5.3.3 Routes of exposure

Some studies reported results based on particular ways of using the powders, such as on feet or perineal use or use after bathing or use on sanitary napkins or use on diaphragms or use by male partners, and so on. And many studies just reported results for all routes of perineal exposure combined. For my Main analyses, I aimed to use the reported results pertaining to all types of perineal use combined. Where the results were reported for individual routes of exposure rather than all perineal use combined, I identified the one that came closest to powdering in the perineal area from all routes.

The number of studies providing results pertaining to any of those specific routes of exposure was much less than the number providing evidence for all routes combined and insufficient to provide reliable meta-analysis results for route-specific estimates of RR. Among the route-specific reports, the one that had most often reported RR results was exposure from dusting of sanitary napkins. I will conduct a separate meta-analysis regarding the risk of ovarian cancer in relation to use of powder on sanitary napkins.

5.3.4 Questionnaire items on use of talc powders

In the case of exposure to cosmetic talc powder, the most common and realistic way of ascertaining exposure has been to question women. But there are many ways this can be done, and indeed many types of questionnaires have been used. A very simple format that has been used is to ask a question such as "have you ever used powders in your genital area?" But, the validity of the response would be enhanced if the question is framed in a more specific manner, so long as the respondent can be expected to know the answer to the more specific question. One possibility would be: "have you ever used powders that contained talc on your genital area more than once a week for at least 6 months of your life? This would include powdering your genital area directly or powdering your underwear or powdering your diaphragm or powdering your sanitary napkin." There are scores of ways such questions can be asked, and there has been variability in the methods of questioning among the different studies of powder use and ovarian cancer. In most studies, the questionnaire question about Ever Use was actually about Ever Regular Use, not Ever Occasional Use.

Among women who used powders, there can be an enormous range of usage from a few occasions in a lifetime to profuse daily usage. Among the many dimensions of talcum powder exposure that might influence the risk of cancer are the following: manner in which the talc was applied, age at which exposure began; if it ended, age at which it ended and years since it ended, frequency of use per day, week or per month, multiple applications including to genitals, undergarments, sanitary napkins, etc., and whether and how that varied at different ages. Some studies have used a single simple question, while others have used scores of questions to get at the lifetime history and many facets of powder use.

While I believe there are quality differences between the different studies in the way talc powder data have been collected, I have refrained from imposing my judgement about the quality of the questionnaire data on the selection of studies to include in meta-analyses.

5.3.5 Metrics of exposure

I used the reported results for the binary metric Ever Regular Use vs Never Regular Use, given the limitations of the available data, and using the investigators' decisions about how best to measure this. While this may seem like a simple tactic to implement, some studies were reported in such a way that in fact I had to make "judgement calls" about which of the reported results came closest to the desired metric.

For "dose-response" assessment, I used three pertinent metrics of exposure: duration (years), intensity/frequency (uses per day, week or per month), and cumulative number of applications, measured sometimes in absolute numbers or sometimes in quantiles. Of the three, the most meaningful is the cumulative number of applications.

6. My meta-analyses regarding talcum powder products and ovarian cancer: data included and results

6.1 Features of the studies

Following the exclusions indicated in Appendix Table A1, **Appendix Table A2** shows the studies that ended up being included in one or more of my meta-analyses, and brief descriptions of administrative and contextual features of each study. **Appendix Table A3** shows, for the same studies, some information about the talcum powder exposure variable and the covariates used by the authors in their control for confounding.

Appendix Table A2 shows that most studies were conducted in the USA. All but three were case-control studies and of the case-control studies, all but four used some type of population control series. Most studies had fieldwork data collection in the 1970's and 1980's; only a few studies started data collection after 2000. Table 3 shows for each study what exposure variable I was able to use to approach the notion of Ever exposed regularly to talc powder in the perineal region. Different studies had different questions in the questionnaire and different studies reported different variables. The questionnaires usually elicited lifetime use that was more than very sporadic, with terms like "regular" use. Only the Gonzalez 2016 study failed to ask about lifetime exposure before the interview; they asked about usage only in the preceding 12 months. The Gates 2010 study

asked about use of talc up to 1982 but not afterwards. Some studies asked separately about different routes of exposure and then rolled them together in statistical analyses, while some rolled all routes of exposure together in their questioning. The term that I show in Appendix Table A3 is the term that the authors reported in their publication of results; it is sometimes rather cryptic. Appendix Table A3 also shows which variables that the authors reported having used as adjustment variables. Sometimes these are variables that were explicitly included in final statistical models, and sometimes these were dealt with in a more indirect way such as a staged analysis in which a screening is conducted using a change-in-estimate procedure.

All meta-analyses were conducted using the well-known package Comprehensive Meta-Analysis Version 3. (Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. Biostat, Englewood, NJ 2013; https://www.meta-analysis.com/index.php?cart=BFZW2135997

6.2 Association between binary variable talc powdering and all types of ovarian cancer combined – data and results

6.2.1 Individual studies and results on binary exposure variable

Table 2 shows RR results, as well as the corresponding 95% confidence intervals, for each informative study included in the Main meta-analysis or in any sensitivity analyses. (I will explain this distinction below.) As I explained in Section 4.1, the single number which reflects quite well the statistical strength of a study, be it case-control or cohort, is the number of exposed cases, and I have included this parameter in Table 2. Table 2 shows the RR reported in each study by Ever (regular) use of powder in the perineal region (all routes of perineal exposure including direct powdering on genital area, on sanitary napkins, on underwear and on diaphragms). The table shows results for all types of ovarian cancer combined.

Before conducting any meta-analyses, we can peruse the results in Table 2 to observe certain patterns.

Of the 33 RR results shown in Table 2, two are below 1.0, one equals 1.0, and 30 are greater than 1.0. On the null hypothesis that there is no true association between powdering with

talc and ovarian cancer, we would expect as many of the RR estimates to be above 1.0 as to be below 1.0. The observed distribution (2 below and 30 above) is clearly and strongly in defiance of the null hypothesis. Further if we rank the RR estimates from lowest to highest, the median value, the one in the middle, would be 1.34.

This informal analysis does not take into account that the 33 estimates in Table 2 are not strictly independent of each other. There are various ways to carve out independent sets of results from this list of results in Table 2, and the meta-analyses will be designed to do that. But no matter how the studies are configured, it will be found that one or two of the RR estimates are below 1.0 and somewhere between 20 and 26 are above 1.0. Such an imbalance cannot be due to chance.

6.2.2 Strategy for Main analysis and sensitivity analyses

An investigator typically has in mind a strategy for analysing and presenting the results. There may be some judgement or assumptions involved in deciding on the strategy. The investigator may wish to see how the results would be affected if other judgements or assumptions were made. In other words, how robust are the results to alternative judgements and assumptions. Such alternative analyses are referred to as *sensitivity analyses*.

There were several dilemmas in selection of studies and results to include in the meta-analysis. I made decisions in each case that I believe provides the best basis for a meta-analysis. But in deference to other possible decisions that might have been made, I conducted some sensitivity analyses as well. I list what the dilemmas were and which options were selected for Main analyses and for sensitivity analyses.

a. Terry 2013 and Wu 2015. The Terry 2013 paper brought together data from 8 different research teams. Some of those teams had previously published their results on talc and ovarian cancer and some had not. Normally, a pooled analysis would take precedence over the individual component studies. In this case, however, there were complicating factors. The Los Angeles component study of Terry 2013 (Wu, Pike and colleagues) was conducted in stages and the Terry 2013 pooled analysis only had access to the early stage. Subsequently, Wu and colleagues carried on with their data collection, and published a

more complete set of results from their study in Wu 2015. The Terry 2013 paper contained 208 exposed cases from the Los Angeles study, whereas the Wu 2015 paper contained 701 exposed cases. In the entire Terry 2013 paper there were 2600 exposed cases. Ideally, we would wish to exclude from the 2600 exposed cases in the Terry 2013 paper, the 208 exposed cases that came from the early Los Angeles data. But that information was not available. Thus there is an 8% overlap between the exposed cases in the Terry 2013 paper and those in the Wu 2015 paper.

I adopted the following strategy. For the Main analysis, I included both Terry 2013 and Wu 2015. The 8% overlap of exposed cases is unfortunate but I believe its impact would be trivial, and in any case we will have some empirical evidence of its impact from a sensitivity analysis.

I conducted sensitivity analyses using a different strategy. The Terry 2013 paper contained a table in which the individual results of the 8 component studies were reported. I used the results as reported there for 6 of the 8 component studies, for which the Terry paper contained the latest results. For the Los Angeles study I used the result reported in Wu 2015 which was much more complete than the L.A. study result in Terry 2013. The eighth study was the study of Cramer that was one of the components of Terry 2013 but that was also reported subsequently in Cramer 2016. It is not clear whether the Cramer 2016 paper contains more up to date data than the corresponding component in Terry 2013, but it possibly does.

To summarize, the Main analysis contained pooled result from Terry 2013 and the result from Wu 2015. There were sensitivity analyses that dropped the pooled result from Terry 2013, but included the (apparent) latest published result for each of the 8 components.

b. Nurses Health Study. This cohort study was initiated in 1976 and was not a study of talcum powder products and ovarian cancer . The study involved a wide-ranging annual questionnaire which inquired about many health related issues. In 1982 there was a very succinct question about use of body powders. The cohort has been followed-up to ascertain the occurrence of cancers (or other diseases). There was a publication that contained results on talc and ovarian cancer from this study in 2000 (Gertig 2000); later, after more

years of follow-up there were two further papers presenting results on talc and ovarian cancer (Gates 2008 and Gates 2010). Clearly the Gertig result did not belong in my meta-analysis, since it was subsumed by subsequent analyses, but the choice between the Gates 2008 and Gates 2010 was not so obvious. Gates 2008 was based on a nested analysis of a subset of the cohort that probably entailed better control for confounding. Gates 2010 was based on the entire cohort and thus on a much larger sample size. The two RR estimates from the Gates papers are quite different from one another (RR=1.24 in Gates 2008 and RR=1.06 in Gates 2010). It is not clear whether the difference in results is due to the different design and analytic procedures used in the two papers. The authors did not comment on the inconsistent results.

My Main analysis included Gates 2010 but not Gates 2008. Some sensitivity analyses contained Gates 2008, but not Gates 2010.

It should be noted that whereas I did not use the Gertig paper results in the meta-analysis of Ever / Never Use of talcum powder products, I did use some dose-response results from Gertig because subsequent publications from the Nurses' Health Study did not present such results.

c. Schildkraut (2016). This was a case-control study of ovarian cancer among African American women. The fieldwork and interviewing was carried out from 2010 to 2015. The authors speculated that publicity surrounding two class action lawsuits on talc and ovarian cancer in 2014 may have subsequently induced bias in the validity of reporting of talc exposure. Consequently, in their analysis and report, they presented two sets of results, one for all women in the study, and another for those interviewed before 2014. It is impossible for me to evaluate the validity of the speculation, as it was for the authors. Consequently I will use the results from the entire sample and those from the pre-2014 sample. I refer to the entire Schildkraut study result as Schildkraut A and the pre-publicity result as Schildkraut B.

The Main analysis contained Schildkraut A. Some sensitivity analyses contained Schildkraut B.

d. Shushan (1996). This ovarian cancer case-control study, conducted in Israel, reported results on talc and ovarian cancer, but the report was quite cryptic regarding the data collection and the talc exposure variable.

The Main analysis excluded Shushan 1996. Some sensitivity analyses included Shushan 1996.

6.2.3 Results of meta-analyses on binary exposure variable for all ovarian cancers

Figure 1 shows the printout from the Comprehensive Meta-analysis (CMA) package for the Main meta-analysis for the association between ever regular use of talc powder in the genital area and all types of ovarian cancer combined. 21 RR results were used in the Main meta-analysis, but the Terry 2013 study represents 8 different study teams and 10 distinct studies. In the forest plot, I have ordered the studies in increasing magnitude of the RR estimate. It can be seen that only one study produced an RR estimate to the left of the null value of 1.0, while 19 studies produced an RR estimate to the right of the null value of 1.0.

The meta-estimate of RR is 1.28 with a 95% confidence limit from 1.19 to 1.38. The p-value is too small to register in 2 digits. This is a very highly statistically significant result. The probability of this result being attributable to chance is vanishingly small.

The 21 RR estimates in this Main meta-analysis had a fairly low p-value for heterogeneity, 0.07, but it was not statistically significant. This means that there was considerable variation in RR results across the studies, but this might have been due to chance. That there is significant variation in RR estimates is not surprising. The different studies were conducted among different populations, using different methodologies. It would be surprising if there was no variation. It is nevertheless true that in the current state of knowledge the best estimate of RR is the meta-estimate of 1.28.

Table 3 shows the results of the Main meta-analysis again and contrasts it with the results of seven sensitivity analyses that embody alternative plausible strategies for selecting studies and selecting results within studies. These alternative strategies had almost no effect. The meta-estimates of RR varied in a narrow range from 1.26 to 1.30. Even the lowest of these would lead to the conclusion that there is a highly significant association.

It can be affirmed, quite confidently, that the apparent overall elevated risk for women who had ever used such powders is not an artefact of chance variation. This conclusion is not new. It has been stated by the authors of previous meta-analyses. However, I believe this conclusion is based on the most current and reliable data now available.

From a statistical point of view, each of the studies listed in Table 2, except for one or two outliers, shows a 95% confidence interval that overlaps substantially with the confidence interval of the meta-RR estimate (1.19 – 1.38). Further, the majority of the study-specific confidence intervals (including 2 of the 3 cohort studies) include the overall meta RR of 1.28. This shows that there are few if any studies that are not compatible with the overall RR estimate.

6.2.4 Other contemporaneous meta-analyses on binary exposure variable for all ovarian cancers

I started to conduct my meta-analyses in 2015 and revised it in 2018. Towards the end of my analyses, I discovered that two other teams of researchers were carrying out meta-analyses on the same topic at almost the same time. The simultaneous and independent conduct of these three meta-analyses provides a unique opportunity to cross-validate the methodologies and results. (I knew nothing about the two others and I assume they did not know either about mine or the other meta-analysis.) It is sometimes portrayed that meta-analysis is a fairly automated procedure which should produce identical results irrespective of who carries it out. This is far from true.

Even before the statistical part of the meta-analysis is conducted, the author of a meta-analysis has to assemble all of the relevant data. That usually consists of two steps: identifying all informative studies on the topic and identifying the relevant result from each study to include in the meta-analysis. There are many ways to do these steps, and it is not surprising that different, equally competent, investigators may make different decisions about how to identify the studies and how to identify the most relevant results. This is particularly true in the area of observational epidemiology research, as opposed to clinical trials research. Research designs and methods of conduct and reporting are much more standardized in clinical trials research than they are in observational epidemiology. In the

area of research on talc and ovarian cancer (which is observational) there are many opportunities for judgement of the author of the meta-analysis to come into play, and in section 5.3.1 I have listed some of the decisions that I made, in the way I managed the selection of studies.

The two other meta-analyses were conducted by Berge et al (2018) and by Penninkilampi et al (2018). They conducted rather different search procedures than I did. Since I had already participated in the IARC review and the Langseth 2008 paper, I already had a head start on collecting the relevant scientific literature. **Appendix B** shows a 3-way comparison of the studies that were included in the meta-analyses by the three authors, and the data from each study that were judged to be most relevant by each author.

As a generalization, it can be seen that the three synchronous meta-analyses identified more or less the same studies and that in general they extracted the same result from each study; but this was not always the case. For my own meta-analysis, I was comforted to note that there was no study that was identified by one of the other meta-analyses that I had missed in my search of the literature (Appendix Table A1).

One of the main points of discordance in procedure was how the three analyses dealt with the Terry 2013 study. Namely, in my Main analysis I used the result of the pooled Ever/Never RR that was quoted by the Terry study, and dropped from consideration the various component studies of the Terry analysis. By contrast, the two others (Berge and Penninkilampi) adopted the strategy of using the results of the individual component studies rather than the overall pooled result. Berge 2018 used the results of the individual component studies as reported by Terry 2013, for most component studies, but for two component studies they used results that were reported in publications that gave results with additional cases. Penninkilampi 2018 also used individual component study results rather than the Terry 2013 pooled result. There are trade-offs between these different approaches. I prefer to use the Terry 2013 pooled result for two reasons. First, a pooled analysis with a standard set of covariates and a standard statistical model is considered superior to a meta-analysis of the components study results. Second, each publication tends to show a variety of results, and the author of the meta-analysis has to choose a

"best" one to represent the "bottom line" from each study. In the Terry pooled analysis, it was the investigators of the original studies, who were also co-authors of the pooled analysis, who chose which would be the "best" result to represent the study, and this in my opinion is more reliable than outside authors making that decision.

Table 4 shows the meta-RR results from each of the three meta-analyses. Notwithstanding the differences in choices and strategies of the three meta-analyses, the meta-RR results are quite similar, ranging from 1.22 (1.13 – 1.30) in the Berge analysis, to 1.28 (1.19 – 1.38) in my analysis, to 1.31 (1.24-1.39) in the Penninkilampi analysis. These three sets of results are really quite close to each other.

The methodology I used is sound and reliable and consistent with the high standards of my discipline. The strategy and decisions I made in relation to the studies selected and the data abstracted from each informative study is consistent with that methodology I use in my professional practice, and that has earned me recognitions and honors throughout the world.

The results shown in Table 4, are in the same "ballpark" as the meta-analysis previously conducted by Langseth 2008 and they are based on a larger pool of accumulated publications. This indicates that recent evidence is consistent with older evidence and reinforces the consistency of the evidence.

6.2.5 Meta-analysis on powdering of sanitary napkins

Tables 2-4 pertain to RRs for the combination of all routes of exposure to the perineum, including direct dusting and dusting on sanitary napkins, diaphragms, underwear, and condoms. When such an exposure variable was not provided in the paper, I used the one that came closest, with priority to dusting on the body directly. Most studies did not report RR results for every route of exposure separately. For the studies that did so, the numbers exposed were much lower than for all routes combined and there was limited statistical power in those analyses. Of the different routes, the dusting on sanitary napkins was generally the most commonly reported route apart from direct dusting. Consequently I assembled the data pertaining to dusting on sanitary napkins and conducted a meta-analysis of those results.

Table 5 shows both the individual studies that had results on sanitary napkin dusting and the meta-analysis result for those studies. The meta-RR was 1.08 (95%CI 0.89 - 1.31), heterogeneity p=0.09. Given the overlap between the confidence intervals between this meta-RR estimate for sanitary napkin powdering and the meta-RR for powdering the perineal area via any route (1.28; 95%CI 1.19 - 1.38), it cannot be affirmed that the result for sanitary napkins is statistically significantly lower than the meta-RR results in Table 3 for all routes of exposure; but the tendency is in that direction.

Berge 2018 and Penninkilampi 2018 also meta-analysed the data on use of powder on sanitary napkins. By contrast with my results, Berge 2018 reported an RR of 1.00 (95% CI 0.84-1.16) and Penninkilampi 2018 reported an RR of 1.15 (95% CI 0.94-1.41). Since their publications do not make it clear which studies and which results were used in these analyses, I cannot see easily what explains the discordance among the three meta-analyses for sanitary napkins powdering. In any case, it certainly appears that the RR was lower for application to sanitary napkins than it was for general perineal application. The interpretation of this finding is not self-evident. The different routes of exposure may entail very different frequency of exposure. For instance, whereas use of powders on sanitary napkins might involve exposure on only a few days per month, regular use on the perineal region often involves daily or near daily application. I am unaware of any evidence that would address the question of whether regular use on sanitary napkins leads to greater or lesser delivery of talc particles to the portal to the ovary than does regular powdering on the perineal region.

In any case, irrespective of the evidence regarding sanitary napkin exposure, the results in Tables 2 and 3 clearly show an association between exposure to talc in the perineal region and risk of ovarian cancer.

6.3 Dose-response – cumulative exposure, duration and frequency

An important part of the evaluation of causality is to determine whether the results display any kind of dose-response pattern. Tables 6 to 8 show results for various quantitative metrics of exposure.

Trends by cumulative exposure: **Table 6** shows results from five publications that presented results based on a cumulative amount metric. Four of the studies were based on counts of numbers of powderings, while the Cook 1997 result was based on counts of the number of days on which powdering occurred. As can be seen by perusing the column of numbers of exposed cases, the Terry 2013 results dwarf the others in terms of the statistical information they contain. The Schildkraut study, with about one-tenth as many subjects as the Terry study, nevertheless has as many subjects as the other three studies combined. The relative statistical power of the different studies is also manifested in the width of the confidence intervals.

The evaluation of the statistical significance of a trend is not a methodologically straightforward endeavour. Of particular concern is the question of whether or not the test for trend among subjects in different "dose" categories should include or exclude the unexposed category. My view is that it depends on whether or not the study results for Ever/Never exposure are part of the buffet of results presented by the authors. Namely, if the only result presented is a dose-response analysis, then it is appropriate to include the unexposed category as part of the study results. If the Ever/Never result is presented and then a dose-response analysis is conducted, it is preferable to maintain statistical independence of the two analyses by excluding the baseline unexposed category from the dose-response analyses. I will interpret the data from these studies in light of this interpretation of trend tests.

The three smallest studies in Table 6 show no evidence of a dose-response pattern. However, the estimates are so imprecise, as evidenced by the very wide confidence intervals, that they are virtually uninformative regarding the presence or the absence of dose-response.

When looking at the Terry 2013 results, which assemble data from eight teams and 10 studies, the confidence limits are much tighter and the estimates of RR much more precise. The p-value for trend (excluding the unexposed group) is 0.17. Nevertheless, with a reference value of RR=1.0 among unexposed, and with point estimates of RR in four quartiles of cumulative exposure of 1.14, 1.23. 1.22, and 1.32, these results are certainly

compatible with the presence of an underlying dose-response relationship. Note that the absence of statistical significance of the trend among the four exposed subsets is not equivalent to the demonstration of an absence of dose-response. Similarly, the Schildkraut 2016 study results, while based on only two lifetime cumulative "dose" categories with point estimates of 1.16 and 1.67, are also compatible with a dose-response pattern.

Trends by duration of exposure: **Table 7** shows the results of those studies that presented RRs by duration of use. The Terry 2013 pooled analysis did not report results by duration of use; however, some of its constituent studies did so and are included here. The numbers in each of the duration categories in each of these studies is quite small, and consequently the RR estimates are very imprecise, with wide confidence intervals. The categorisation of duration differed quite a bit among the studies and it is not easy to compare results between studies. There is no indication of a dose-response relationship in these results. Though, the wide confidence intervals make it impossible to affirm that there is evidence against dose-response. Further, the largest study showing results by duration of use, Wu 2015, did find a significant increase in risk with increasing duration.

Trends by intensity of exposure: **Table 8** shows results of those studies that reported by intensity (i.e. frequency) of usage. This ignores duration of usage. Like the results in Table 7, the results in individual studies are based on rather small numbers and they entail imprecise estimates of RR. Also like Table 7, the pattern of results is equivocal. There is no clear evidence for or against an underlying dose-response.

The Berge 2018 paper also looked at dose-response. They only looked at trends by duration of usage and frequency of usage, analogous to my Tables 7 and 8. However they actually fitted continuous variable models and found that there were significant trends in risk by duration and by frequency of exposure. They did not examine trends by cumulative exposure, and in particular they did not use the results from the Terry 2013 pooled analysis, which in my view is the most informative evidence available on dose-response.

Penninkilampi 2018 looked at risk according to long duration of usage and found no trend. They also looked at cumulative exposure with total number of applications, and they reported a slightly higher RR for women with greater than 3600 applications (RR=1.42)

compared with women who had fewer than 3600 applications (RR=1.32). I cannot determine from the paper which studies were included in this analysis and in particular whether the pooled Terry 2013 dataset was included. While the Terry 2013 and Penninkilampi 2018 papers both contained some results on dose-response, they are not included in Tables 6-8 because they are not original data collection studies; like mine, their's is a review of other studies which are contained in Tables 6-8.As indicated above, all other things being equal, the best metric of the three quantitative ones is the cumulative exposure metric, and that is the one that happens to provide the most statistically reliable data. Thus, the evidence from Table 6 overrides the weaker evidence from Tables 7 and 8. The evidence from the Terry 2013 paper is the most important piece of evidence we have on dose-response. The evidence from the Terry 2013 paper is compatible with the presence of a dose-response relationship between use of powder and ovarian cancer.

6.4 Subtypes of ovarian cancer - in particular, serous invasive tumors

Most studies that provide results on RR between talc powder and ovarian cancer provide results for all types of ovarian cancer combined. Less than half of the published studies have also provided results of the associations between talc powder exposure and various subtypes of ovarian cancer.

To the extent that talc exposure might have different effects on different subtypes of ovarian cancer, there would be a clear advantage to segregating the evidence by type of ovarian cancer and evaluating the evidence for each subtype. The serous-invasive subgroup comprises over half of all cases, and the rest are split among several other histology-behaviour subgroups (mucinous, endometroid, clear cell, others, and these can be further subdivided by invasive or borderline). Those latter subgroups entail very small numbers each and barely provide enough data, in most studies, to produce informative risk estimates. In those studies, where results were presented by histologic-behaviour subgroups, it is my judgement that there is no strong consistent pattern indicating that one subtype has higher risk than another. Of course, there is variability in point estimates of RR, but on the one hand the variability in RR estimates between ovarian cancer subtypes within studies is not greater than would be expected from chance variability (mostly, the

confidence limits overlap considerably), and on the other hand, from study to study, it is not always the same subtype that seems to have the highest or lowest relative risks.

In the largest assembly of cases subdivided by histologic subtype, the Terry 2013 pooled analysis, the results by subtype were as follows:

- Serous: n=1197; RR=1.24(1.13-1.35)
- mucinous: n=94; RR=1.06 (0.82-1.36)
- endometroid: n=304; RR=1.20 (1.03-1.40)
- clear cell: n=187; RR=1.26 (1.04-1.52).

Other than serous invasive tumors, there is no other subtype for which there are sufficient numbers of studies and sufficiently precise estimates of RR in each study to provide reliable estimates of the overall RR. While the results for endometroid and clear cell tumors show risks that are closely aligned with those for serous tumors, the result for mucinous tumors are so imprecise, because of the very small numbers of such tumors, that the estimated RR of 1.06 is very unreliable.

Consequently, and because there were multiple studies apart from Terry 2013 that presented results for serous tumors, I decided to conduct a meta-analysis for serous/invasive ovarian cancers, but not for other subgroups. The meta-analysis on serous invasive tumors will indirectly inform us also about the relative risks for other types of ovarian cancer. Namely, if the RR for serous invasive tumors is similar to that for all ovarian tumors, it will imply that the risks for other types (the complement of serous invasive tumors) will not be very different from the overall RR. If the RR for serous invasive tumors is much greater than that for all ovarian tumors, it will imply that the risks for other types (the complement of serous invasive tumors) are lower than the overall RR. Similarly, if the RR for serous invasive tumors is much lower than that for all ovarian tumors, it will

imply that the risks for other types (the complement of serous invasive tumors) are higher than that for all ovarian cancer.

Table 9 shows all the studies that reported results concerning the link between talc exposure and serous/invasive tumors. There were 8 informative studies, including Terry 2013, which carried by far the most statistical weight. The meta-RR estimate for serous/invasive tumours was 1.25 (1.1.15- 1.36). This is very similar to meta-RR for all ovarian tumors, albeit based on a smaller number of informative studies. Thus there is no persuasive evidence in these studies, taken as a whole that the effect of talc differs by histologic subtype of epithelial ovarian cancer. That is, with such a tiny difference in RRs between that for all ovarian cancers combined and that for serous invasive ovarian cancers, it can be safely inferred that the RR for other types of ovarian cancer (the complement of serous invasive) would not be far from the overall RR of 1.28.

6.5 Conclusion from meta-analyses and dose-response considerations

My opinion, based on up-to-date data and meta-analyses, is that the RR between ever perineal use of talcum powder products and ovarian cancer (all types combined) is 1.28 (95%CI 1.19-1.38). This result is highly statistically significant.

We can rule out random variability as a possible explanation for the apparent excess risks.

Further, the examination of results according to the "amount" of exposure, and notably the cumulative exposure variable used by Terry 2013, shows that the higher the exposure, the higher the risk.

Such a pattern of findings can have only two possible explanations: it must be the result of some sort of bias or confounder that operated in multiple studies or it must be the result of a real causal association.

7. Misconceptions and possible biases

In reaching my opinions, I have objectively looked at the data and scientific literature and considered the points of view of others who do not share the conclusions I have reached. There are generally two sources of disagreement: misconceptions of epidemiologic or

statistical concepts which I address below in Section 7.1 and professional judgement of the likelihood of errors and biases in the various epidemiological studies, which I address in Section 7.2.

7.1 Some prominent misconceptions in reviewing the evidence

Table 10 lists some prominent misconceptions, and I will address them here.

Misconception: "Cohort studies are more valid and informative than case-control studies."

As can be seen in Table 2, the case-control studies tended to produce higher RR estimates than the cohort studies. It has sometimes been claimed that cohort studies are more valid than case-control studies. There is no theoretical or practical reason why such a blanket assertion should be universally true. There are many factors that influence the validity of a particular result in a particular study and it cannot be reduced to any simplistic assertion that cohort studies are more valid than case-control studies, or vice versa. In the next section, I will go through a number of potential sources of distortion of results from epidemiologic studies, and I showed that some of them might occur in cohort studies, some in case-control studies, and some in both. Some of these distortions very likely occurred in some or all of these studies that provide data on talc and ovarian cancer. On balance, I believe the results of each of these case-control studies concerning female use of powders and ovarian cancer are credible, and perhaps more so (for reasons given in section 7.2), than the analogous results of each of these cohort studies.

Misconception: "Hospital-based case-control studies are more valid and informative than population-based case-control studies."

In a case-control study, the design objective is to define a study base, or a population base, in which the cases might occur, and to identify representative samples of cases and of controls in that study base. The purpose of a control group is to provide an estimate of the prevalence of exposure to the factor under study in the base population that gave rise to the cases. In many instances, the best source of controls for case-control studies is a population list of some sort. But sometimes using a population list is not feasible or

desirable, and an alternative can be to select controls from among hospital patients with conditions other than ovarian cancer. This was done in some of the ovarian cancer case-control studies.

The most common generalization made by epidemiologists is that population-based case-control studies are more valid than hospital-based case-control studies. In fact, neither this nor the opposite statement that I articulated as a Misconception, is universally correct. Validity of a case-control study depends on the specific design features and circumstances of the study.

It is possible that some types of hospital controls have patterns of usage of powders that are different from those of women in the general population, either because the powders are actually causally associated with the diseases that those women have or because their disease or condition that led them to be hospitalised induces some women to take up the use of such powders. If such a mechanism was present in a hospital-based case-control study, it would likely lead to an artificially attenuated RR, not an artificially inflated RR.

Misconception: "Counting the number of statistically significant results is a valid way of assessing consistency of results among multiple studies."

This misconception betrays a lack of understanding of statistical significance. As can be seen in Table 2, several of the individual studies listed in my meta-analysis did not find a statistically significant increase in RR. This has been cited by some as evidence that there is no real causal link.

In fact, meta-analysis is a method that was developed precisely because counting significant results is an invalid way of synthesising knowledge. Namely, a result from a single study may fail to achieve statistical significance either because there is no risk in that study, or because the statistical power of the study was limited. Meta-analysis was developed in order to combine evidence from multiple studies that may be under-powered on their own, but when combined show an effect that might be statistically significant. The meta-analysis cannot conjure a statistically significant meta-RR if the individual study RRs do not systematically lean in the direction of an excess risk, and they do so in the area of talc and ovarian cancer to a degree that cannot be explained by random fluctuation.

Misconception: "You cannot prove causality with an RR less than 2.0."

There is nothing in epidemiologic theory or practice that justifies such a statement. Indeed, this assertion about an RR $\geq$ 2.0 threshold does not exist in epidemiology. There are many well-established causal relations where the RR is less than 2.0. Table 11 lists a number of such examples. In clinical medicine also, it is very common to strive to find therapies that reduce the risk of death from some disease by as little as 10%, and several such discoveries are well documented and have been integrated in medical practice, even though the change in risk is small.

Misconception: "If a product has been used for a long time it must be safe."

It has been argued that since talc powder has been used for many decades by millions of women (and men and children), it has stood the test of time and should be considered safe. This is a specious argument.

Most agents in our environment or in our lifestyle which are now considered dangerous were used for decades or centuries without falling under a cloud of suspicion. These include such factors as cigarette smoking (many cancers and cardiovascular disease), asbestos (lung cancer), sunlight (skin cancer), ingesting very hot liquids (esophageal cancer), and many others.

Misconception: "Government agencies provide the most reliable and authoritative statements regarding the lack of carcinogenicity of talc."

Various national and international agencies have websites which list carcinogens. Examples are: National Cancer Institute (NCI), National Toxicology Program Report on Carcinogens (NTP-RoC), International Agency for Research on Cancer (IARC). It can be argued that these agencies, which undoubtedly have scientific credibility, would not put on their websites information that is out of date or invalid. However, that claim is false.

IARC has a rigorous evaluation process which is considered quite authoritative throughout the world, including in the U.S. But the evaluation is carried out at a certain point in time. The last time talc was evaluated by IARC was in 2006. Based on the evidence available then, the panel rated talc as a "possible" carcinogen. Additional evidence has been accumulated

and come to light since then, but there has not been a new evaluation by IARC. (There are potentially thousands of agents to evaluate, and IARC has resources to only evaluate a few each year. Thus they cannot keep re-evaluating the same ones as soon as new evidence is published.)

NTP-RoC is a congressionally-mandated program whereby the agency is obligated to periodically publish lists of known and suspected carcinogens. Unlike IARC, it appears that the people who make the decisions are internal RoC scientists, rather than external experts, with advice from outside experts. Also unlike IARC, the biennial reports only contain listings of those agents that have been deemed to be definite or likely carcinogens, so there does not seem to be a statutory listing of all agents that have been considered. From the minutes of a meeting of the Board of Scientific Counsellors of NTP held in 2000, it appears that the issue was deferred. I am not aware that the RoC has conducted a subsequent review of talc; although, when renominated in 2004, NTP deferred to IARC.

NCI provides a website for doctors where they indicate for each type of cancer, what are the known risk factors. Based upon my understanding, they do not carry out a rigorous evaluation along the lines of the IARC evaluations or even the NTP evaluations. It is a rather superficial process compared with the IARC process and it depends on the existing knowledge of the committee members which in a short time opines about possible associations between each of the scores of cancer types and scores of potential risk factors. This is not to argue that the members of these committees are less expert than the members of the IARC committees, but the NCI committee members have a short time (apart from their main jobs) to review hundreds of possible factor-cancer associations, whereas the IARC committee members have weeks to review just a few.

Scientists and public health agencies regularly consult the IARC evaluations and those of the NTP. The NCI website for doctors is not considered an up-to-date and cutting edge source of information. This is, of course, no reflection on the gravitas of the NCI as a whole, which has much more invested in its original research mission than in its website for doctors.

There are other organizations which may put some information about causes of cancer on their websites. Importantly, I have not seen any agency or organization, including the FDA, that conducted a rigorous evaluation of the epidemiologic and non-epidemiologic studies like we did at IARC in 2006.

Misconception: "A biological mechanism must be proven before we can establish causality"

There are innumerable examples in medical history of discoveries of risk factors or treatments that did not require knowledge of the mechanisms of pathogenesis in order to determine causality. I have compiled a few such examples from medical history and show them in **Appendix C**.

Very often, the initial suggestion was met with scepticism from the vantage point of biologic plausibility. In fact, very seldom have the essential features of biologic plausibility been worked out by the time the epidemiology has convincingly demonstrated that the association is causal. This can be asserted for the early discoveries such as the cancer causing effects of certain chemicals in dye production facilities, certain metals in various heavy industry facilities, certain emissions of combustion of fossil fuels, ionising radiation, and even cigarette smoking. In most of these examples, it was decades after the epidemiologic evidence became convincing that credible mechanistic theories were proven; though, for some, the biologic mechanisms remain unknown.

Indeed in the guidelines of the IARC Monographs, it is stated that if there is "sufficient" evidence of a risk of cancer from epidemiologic studies, then irrespective of the evidence from animal experimentation and other biologic evidence, the agent in question should be considered a Group 1 carcinogenic agent. My point here is that the demonstration of a proven biologic mechanism is not a prerequisite for demonstrating that an agent is a human carcinogen. Reliable empirical epidemiologic evidence of an association is a sufficient basis for demonstrating causality; the presence of a credible biologic mechanism enhances the degree of proof, though that often lags decades behind the general recognition of causality, as exemplified by the examples in Appendix C.

It is not my opinion that we should ignore or set aside consideration of biologic plausibility. As Hill (1965) indicated in outlining the thought process for establishing causality, biologic plausibility is one of the dimensions to be considered. But, he also cautioned that, "this is a feature I am convinced we cannot demand". Thus, as I have done in other contexts in regard to other putative carcinogens, I am able to draw causal inferences about talc irrespective of whether a causal mechanism has been proven.

Misconception: "Bradford Hill criteria comprise a checklist of necessary conditions"

As I explained in section 4.2, the "aspects" that Hill listed are not "criteria" and they are not necessary. This point has been made and is widely accepted by epidemiologists. The list of "aspects" in Hill's original paper have been rephrased and reworked in many textbooks and by most agencies that refer to them. They provide a framework and not a checklist.

7.2 Alternative explanations - Biases and errors

Before inferring that the strong statistical evidence that use of powder in the perineal area by women is associated with ovarian cancer may represent a causal relationship, I considered alternative explanations for these observations. In this section I will consider a number of potential sources of distortion of the risk estimates, under various rubrics. Some of the potential sources of distortion are unique to cohort studies, some are unique to case-control studies, and some can affect both types.

7.2.1 Bias due to non-response or non-participation

This is a potential source of bias in case-control studies.

Among all potential cases and controls who meet the study's eligibility criteria, some participate and some don't. The most common reasons for non-participation are: refusal; inability of the researchers to contact the person because they moved or are too sick or died or are otherwise unavailable; if access to the subject is via the treating physician or medical staff, there could be obstacles at that level. If the factor under study, hygiene powder use, is correlated with the likelihood of participation and if the participation rate is low, this could lead to biased estimates of RR. Such bias could artificially inflate or deflate the RR depending on how the various variables are related to each other. If response rates

are low, say below 70%, and differential both by case-control status and by exposed – non-exposed status, this could lead to biased RR estimates. For such a bias to explain the outcomes seen, it would require quite strong associations between likelihood of participation and powder use, and quite strong differences in such associations between cases and controls. In my opinion, it is very unlikely in the context of these studies that response rate differentials would be great enough to induce such large bias.

7.2.2 Recall or reporting bias

This is a potential source of bias in case-control studies.

Because the exposure history is collected retrospectively, it is subject to both non-differential recall errors (see below), and to recall or reporting bias between cases and controls. Cases and controls may have different motivation and proclivities to recall and report use of powders. If it were true that cases had a greater tendency to over-report powdering history or if controls had a greater tendency to under-report powdering, then this would lead to an artefactual exaggeration of the RR.

There are a few possible causes of such differential reporting. First, it might be hypothesized that there is a general tendency for cases in case-control studies to acknowledge behaviours or exposures with much greater frequency than controls just because they are more invested in the research than are controls. They may wrack their brains during the interview to find instances of the queried behaviour or exposure that controls don't pay much attention to during the interview, because the controls just "want to get the interview over with". If this were the case, we would systematically see elevated RRs from case-control studies for all manner of variables in all kinds of studies. But in my experience, this does not occur. (I have conducted many case-control studies, each study eliciting information on many lifestyle factors and exposures. It has not been the case that cases systematically report more exposures than controls.) Furthermore, and more pointedly, if such a phenomenon were operative in these case-control studies of ovarian cancer, we would see elevated RRs when women were questioned about the use of powders on other parts of their bodies than the perineal area. In fact, several studies did ask such questions. In the Terry 2013 analyses, based on very large numbers of women, the

overall RR for ever use of hygiene powder on non-genital areas of the body was 0.98 (0.89-1.07), in stark contrast to the analogous result for genital use of 1.24 (1.16-1.33). In other words, when questioned about powdering in non-genital areas, controls were as likely to say "yes" as cases. Clearly there was no tendency for cases to indiscriminately report exposures more frequently than controls.

A second possible reason for such a situation to arise is if there was widespread knowledge about powdering being under suspicion for ovarian cancer. In such a situation women who have heard about this might internalize the notion that powdering may have caused their cancer, and they might ruminate with such intensity on the notion that they might imagine that they had used powders at some point in the past. But for most of the period of data collection in these studies, there was very little public discussion of a possible linkage between powdering and ovarian cancer and I doubt if more than a handful of the thousands of women interviewed in these studies would have heard of such a hypothesis before being interviewed.

In my opinion recall bias is not likely to have produced the kinds of RRs we see in these studies.

7.2.3 Non-differential (or random) error in recall or reporting of exposure to powders

This is a potential source of bias that would affect both case-control and cohort studies, but not exactly in the same ways.

Reporting past history of activities and exposures is always subject to some degree of error; it can result from ambiguity or misunderstanding of the questions, failures of memory, or inattention. And this is certainly true for history of powdering. If such error is non-differential (i.e. equally present for cases and controls in the case-control context) it has an effect on RR estimates that is rather predictable. Namely, as I explained above, it has the effect of artifactually decreasing the RR. The degree of attenuation is roughly proportional to the degree of error or misclassification. If there really is a causal association between powdering and ovarian cancer, then we can be rather certain that the true RR is higher than what we can see in the various studies that have reported RRs.

Furthermore, we might make some reasonable inferences about the impact of reporting error on dose-response trends as well as on the overall RR. It is reasonable to surmise that the amount of reporting error is quite a bit higher for the details of past usage (duration of usage, intensity and frequency of past usage) than it is for the simple fact of usage. That is, there is less error in a woman's report of whether or not she ever used powders on a regular basis than in her report of the details of the usage, even if powdering behaviour may be a relatively stable habit. The consequence of this is that the RR based on ever/never usage (Table 2) is less subject to artefactual attenuation than the RRs based on categorizing the duration or intensity or cumulative amount of usage (Tables 6-8). This is a possible explanation of why there has been a much clearer signal of elevated RR for ever/never usage than there has been for dose-response.

There is likely to be more measurement error of exposure to powders in cohort studies than in case-control studies, for several reasons. First, because the cohort study questionnaires attempted to broach topics that could be relevant to many types of cancer and indeed many diseases, the questions posed in the cohort study questionnaires about talc powder use tended to be much briefer and probably less effective at eliciting valid information than the questionnaires used in case-control studies of ovarian cancer. For instance, the cohort studies did not elicit information on timing or duration of past usage, and one of the cohort studies did not even attempt to elicit information about use of talcum powder products over 12 months before the interview. Second, whereas a case-control design involves a woman looking backwards over her life from the time of incident cancer onset and thereby addressing the entire relevant period of potential exposure, the woman in a cohort study reports on her past usage as of a certain point in her life, but there may be 10-20 years subsequent in which her habits could have changed, and of which the cohort study has no knowledge. The women in the cohort studies were "locked into" their exposure category at baseline of the cohort study. If there were women who in fact started using powders after the baseline, they would be incorrectly labelled as non-users. And, if there were indeed a risk associated with use of talc powders, the risk estimate would be diluted by the incorrect inclusion of users among non-users. Accordingly, the longer such subjects are followed, the more likely such misclassification is to occur.

The age at which information is collected is a relevant consideration. In most case-control studies, the mean age of the study subjects was between 50 and 60. In the NHS cohort study the mean age at baseline questionnaire was around 40 and in the WHI it was over 60. In each study, women were asked about their past history of powder usage. Clearly the WHI women had a further stretch of time to consider than the women of the NHS and even of the case-control studies.

A particular form of measurement error may well have occurred in the Gonzalez 2016 study and produced even more attenuation of RR estimates. Namely, in their brief questionnaire on talc exposure, the question was formulated to ask women about their use of powders in the 12 months preceding the interview. While exposure to talc over the past 12 months may be correlated with exposure over the entire etiologically relevant period, which might go back decades in the life of the woman, the correlation is probably weak, and this is another source of measurement error.

7.2.4 Short follow-up periods for disease ascertainment

This is a potential source of bias that would affect cohort studies.

In a cohort study, if the period of follow-up after baseline is relatively short; and if the latency period between exposure and cancer is long, the excess risk may not be detectable because cases that would occur after long latency have not had time to occur. If this did occur, it would lead to an artificially low RR estimate.

This could have been an issue in the initial publication from the NHS, the Gertig 2000 paper. As of the Gates 2008 and Gates 2010 analyses of the NHS, the follow-up period was probably long enough and this bias should have abated. For the WHI study it was likely an issue in the Houghton 2014 paper, and it would remain so until there is much longer follow-up. It would also be an issue in the Gonzalez 2016 paper from the Sister Study, which had only 6 years of follow-up after exposure was ascertained.

7.2.5 Diagnostic error

This is a potential source of bias that would affect both case-control and cohort studies, but not exactly in the same ways.

The diagnosis of cancer is never error-free. And details of histology and staging are even more error-prone. Further, there are trends in diagnostic criteria and methods over time, as well as in the terminology and classifications used. So what we observe in these various studies of ovarian cancer represents imperfect estimates of true biologic/pathologic status. The impact of such "errors" is mainly the same as exposure measurement error, namely it would tend to artificially reduce RR estimates. Since most case-control studies start from hospital-based cancer diagnoses as the point of entry, they usually have reasonably valid diagnostic information.

In general, cohort studies tend to be more vulnerable to this source of error and bias, because disease diagnosis information is often obtained from sub-optimal sources, such as the information provided by the study subject or her family, or information obtained from death certificates. In the three cohort studies included in the meta-analysis, there were high quality verifications of diagnostic information that had been provided by the women or their families. But such verification may not be as reliable as information coming straight from hospital pathology or oncology services. I expect that this was not a major issue here, but to the extent that it did operate, it too would have led to some additional attenuation of RR estimates, as I explained above.

7.2.6 Initiation of powdering as a result of ovarian cancer

This is a potential source of bias that would affect case-control studies.

It has been speculated that women with early symptoms of ovarian cancer might take up the use of powders to help with relief of their symptoms. If so they might report that they used powders before their cancer was diagnosed and this could artificially inflate the RRs. While the women are usually questioned about the period before their cancer was diagnosed, there could be some "telescoping" so that women who start dusting after diagnosis respond in the affirmative to the questionnaire.

In the same vein, it has been speculated that treatment for ovarian cancer might produce side effects that could be relieved by powdering. And again, it might be posited that women ignore the instruction to refer the exposure question to the time before the onset of the cancer.

If the early symptoms of ovarian cancer provoke some women to start dusting the perineum to relieve some of the discomfort, or if the treatment provokes women to start dusting, this would lead to an artefactual excess RR.

I have not found any empirical evidence to support this hypothesis.

In the few datasets I have seen which describe the age distribution of initiation of powdering, there were very few patients who started in the year or two before diagnosis of the cancer. I am inclined to believe that it is virtually a non-issue, and that if it operated at all, it would only have operated on a handful of the thousands of women who were part of the various case-control studies.

7.2.7 Confounding

This is a potential source of bias that would affect both case-control and cohort studies.

If women who use powders are also more likely to be exposed to other risk factors for ovarian cancer, then it might distort the relationship between powdering and OC. The direction and the degree of distortion (bias) that would be induced depends on two components, a) the true association between the confounder and ovarian cancer, and b) the association between the confounder and dusting behaviour. Thus, depending on the direction of these two component associations, the confounding can result in artificially decreased or increased RRs. Typically, the degree of confounding is much lower than the strength of the association between the confounder and ovarian cancer. In order for a confounder to induce an artificial RR of 1.25 for dusting, it would have to have an RR much greater than 1.25 with ovarian cancer and a fairly strong correlation with dusting behaviour. Given that the main studies have controlled for the main risk factors, I consider it unlikely that this operates. Table 1 shows the covariates that were controlled for in each study, and while there is some variability between studies in the list of covariates, the main known potential confounders (age, BMI or weight, parity) have been controlled for in almost all studies. It should be noted that while smoking is a well-established risk factor for many types of cancer, it is not a risk factor for ovarian cancer; thus, there is no need to control for smoking status in studies of ovarian cancer.

A thorough and reliable investigation of potential confounders was conducted by Cramer (2016); in the large database of New England-based studies, they explored the potential confounding effect of a host of personal characteristics including demographic, reproductive, hormonal, comorbidities, activities, and exposures. None of the covariates that they explored had any meaningful confounding effect on the association between talc and ovarian cancer.

7.2.8 Publication bias

This is a potential source of bias that would affect case-control and cohort studies.

This refers to the tendency for some evidence never to "see the light of day". Namely, when results are "negative" or "null", it may be that investigators never bother to submit them for publication, or alternatively, that editors refuse to publish them. This happens, most likely, when the hypothesis under study is not particularly topical or controversial, and when the study is small. In the talc-ovarian cancer literature this would have been more likely in the pre-2000 era when there was much less scientific interest in the hypothesis linking talc to ovarian cancer. As a sensitivity analysis, I conducted a meta-analysis on the subset of studies in Table 2 that had at least 20 exposed cases. That is, I eliminated the studies from that stratum of the universe of studies that were most susceptible to publication bias. The resulting meta-RR was almost identical to those shown in Table 4. Because this has been a somewhat controversial topic in epidemiologic circles over the past 20 years, I doubt if there were large important studies with null findings on talc-ovarian cancer that went unpublished.

In their meta-analyses, Berge 2018 and Pennikilampi 2018 both showed funnel plots of the results. These are meant to detect so-called publication bias. Both of those analyses concluded that there was no publication bias.

In summary, I consider that the observed association between talc and ovarian cancer is not an artefact due to publication bias.

7.2.9 Summary comments regarding biases and errors

While the results of epidemiologic studies strongly supports the hypothesis of an association between perineal use of powders and risk of ovarian cancer, we must be wary of potential sources of error and bias that can distort an association before concluding that this association is causal. I have therefore gone through the plausible sources and types of error and bias that could potentially explain the positive association seen across the relevant studies to ascertain how likely it is that each such type was actually operative and, if so, what the nature of the impact may have been. These evaluations are based on my professional opinion as an epidemiologist having conducted, reviewed, and evaluated many hundreds if not thousands of epidemiologic studies.

Of the various types of error listed, some could artificially inflate the RR estimates and some could artificially decrease the RR estimates. Some are likely to have occurred and some are unlikely to have occurred. The one that certainly occurred and that has a non-trivial attenuating effect on RRs is random exposure misclassification (section 7.2.3). As explained above, if there is a true association, then the true RR is almost certainly greater than the estimates seen in these studies and in the resulting meta-analyses. Other types of error and bias that are highly likely to have occurred are the two that are specific to cohort studies. Namely, the Nurses' Health Study papers (Gates 2008 and Gates 2010) almost certainly suffered from an attenuated RR estimate because of the compromised reference category of "unexposed" while the Women's Health Initiative paper (Houghton 2014) and the Sister Study paper (Gonzalez 2016) almost certainly suffered from a too short follow-up period (section 7.2.4). In my opinion, the occurrence and the possible impact of other listed types of bias and error are more speculative, and less likely.

Consequently, in my opinion, the observed association between talcum powder products and ovarian cancer is unlikely to be explained by any methodological problems with the studies.

8. Bradford Hill guidelines applied to talc and ovarian cancer

The Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) states: "There is no formula or algorithm that can be used to assess whether a causal inference is

appropriate based on these guidelines." These guidelines are simply aspects that might be considered in assessing causality. I will give my assessment of how the evidence regarding talcum powder products and ovarian cancer fit into those aspects. I will use the version listed in the Reference Manual on Scientific Evidence. While there is no objective basis or scientific precedent or "scientific jurisprudence" for quantification or weighting of the various "aspects", to help the reader to understand the relevance that I attached to each "aspect" in my evaluation, I will provide an informal ranking of the importance that I attach to each aspect, in the specific context of the assessment of causality of evidence regarding talcum powder products and ovarian cancer. I will list the aspects in descending order of importance that I attach to them.

My opinions are briefly summarized in **Table 12**.

Highly important aspects in my weighting

There is a set of B-H aspects that are utterly inter-related and cannot be disassociated one from the other. In combination, they represent the most important aspect to consider in evaluation of causality of talcum powder for ovarian cancer. These include strength of association, dose-response, consideration of biases, and consistency of findings.

Strength of the association. This can embody both the magnitude of the RR and its statistical significance. The meta-RR estimate is 1.28. That means that the best estimate from the epidemiologic literature is that women who regularly used talcum powder products in the genital area had 28% higher risk of ovarian cancer than women who did not use such powders. As I illustrate in Table 11 with a few examples, this RR is in line with many well-recognized risk factors for cancer and other diseases. For example, it is well accepted now that people living in an urban neighborhood in which the air is highly polluted with particulate matter have between 5% and 10% excess risk of lung cancer compared with people living in a less polluted urban neighborhood. Also, it is well accepted now that workers exposed to a solvent called trichloroethylene have about a 40% higher risk of kidney cancer compared with workers not exposed to trichloroethylene. Thus, the 28% increase of ovarian cancer for women who used talcum powders is in line with many recognized risk factors. This increased risk as manifested by the meta-RR is highly

statistically significant. (Note that the statistical significance of individual studies is irrelevant to the consideration of causality; it is the totality of evidence embodied in the meta-analysis that counts.) Such a high and significant meta-RR could not have occurred by chance. This is a very important factor in how I view the evidence of causality, and it supports causality.

Dose-response relationship. If the relative risk increases when the exposure increases, it enhances the likelihood that the observed association is really causal. In studies of lifestyle habits like use of talcum powder products, the most common way is to estimate the RR in increasing categories of exposure metrics such as duration (years) of usage, or intensity of usage (frequency per day or per week or per month), or cumulative amount of usage (a combination of duration and frequency). The most sensitive of these metrics is the cumulative amount. I evaluated the published studies reported on risks according to the different metrics. By far, the most important set of results on dose-response is that from the Terry 2013 pooled analysis of 10 studies using the cumulative exposure metric. And, the next most important from a statistical weight point of view is that from Schildkraut 2016. In both of those studies, there is a clear indication of increasing risk with increasing cumulative exposure. Since the statistical power to detect a trend is less than the power to detect an overall risk, it is not surprising that the p-value for trend does not attain the conventional 0.05 level, but it remains true that these studies support a dose-response. This is an important consideration in my assessment of causality, and the evidence on dose-response that our IARC committee had available in 2006 was much less persuasive than the evidence available now.

Consideration of alternative explanations - absence of bias. There are many potential sources of bias in observational research, including in epidemiology. It is important to consider the presence of bias in each study performed or reviewed in an evaluation of causality. The possibility of bias is so multifaceted that it is impossible to reliably assign an explicit score to the likelihood of bias in a study or in a body of studies. It is also important to understand that identifying a potential source of bias is not tantamount to identifying the presence of bias. In section 7.2, I have reviewed the potential role of several types of biases and errors

that can bedevil such research. I concluded there that none of those factors would cause the apparent associations.

Consistency of findings between studies (or replication of findings). Because epidemiologic research is susceptible to errors from random variability and from different kinds of study biases, before accepting the apparent association as a generalized phenomenon, it is important to see that similar results are replicated in different studies. When these different studies also encompass different study populations in different communities, it enhances the generalizability of the inferences. Generally speaking, the observation of consistent results in different studies adds to the credibility of an inference that there really is a causal relationship. In my review of the published epidemiological studies and meta-analysis, I am impressed by the consistently elevated risk across studies. Almost all of the 30 or so studies have produced an RR greater than the null (neutral) value of 1.0. If there really were no association between talcum powder use and ovarian cancer, we would expect to see as many RRs lower than 1.0 as higher than 1.0. The pattern we see is like flipping a coin 30 times and getting a heads 28 or 29 times. The individual study RRs are not all necessarily statistically significant, but that is irrelevant because most individual studies did not have sufficient statistical power to detect RR in the range of 1.2-1.4. It is the statistical significance of the meta-RR, representing the combined evidence that has the requisite power, and that excess RR is highly statistically significant. I place great weight upon this evidence of causality and, here, believe it to be amongst the most important findings.

Moderately important aspects in my weighting

Temporal relationship. Exposure should be seen to have preceded disease. It is almost a logical truism. This is the only aspect that Bradford Hill considered to be necessary. In all of the studies I reviewed, the information elicited about talc exposure concerned the time period before cancer onset. Since it is so obviously important, the reader may wonder why I place lesser weight on this aspect. It is simply because the presence of this condition of temporality is so obvious in these studies.

Biological plausibility (coherence with existing knowledge). It is both conventional and natural to consider whether any putative association is biologically plausible. The notion of

biological plausibility is multi-facetted. In the case of talcum powder products and ovarian cancer, it can include such issues as: how such powders have been used, female anatomy and physiology, toxico-kinetics and toxicology of talc, in vitro and in vivo mechanisms of carcinogenesis, and others.

The first thing to note about this aspect that Bradford Hill listed is that it is called “biological plausibility”, not “biological proof”. That is, there was never any implication that a determination of causality should rest on a demonstrated proven biological mechanism. Hill was always reserved about this aspect, stating that it was not an essential prerequisite to establishing causality. As I have mentioned above, it has been common in the history of medicine and epidemiology for the elaboration of a validated biological mechanism to come much later than the discovery and demonstration of a causal association. Appendix C gives a handful of such examples but there are scores more.

Insofar as the issue of talcum powder products and ovarian cancer is concerned, there is evidence to support a few biologically plausible mechanisms. First of all, there are two possible routes that talcum powder products can take to reach the ovaries. There is published evidence that talcum powder products (and its constituents and contaminants) that are applied to the vaginal area can migrate from there to the fallopian tubes and ovaries (Venter 1979; Henderson 1986; Heller 1996) or to pelvic lymph nodes. (Cramer 2007) In addition, as has been hypothesisized and partially demonstrated in the discussion of asbestos and ovarian cancer, such particles might reach the ovaries via inhalation and translocation. (Miserocchi 2008; IARC 2012) Once the particles reach the ovaries, carcinogenesis can be triggered by the inflammation engendered by the particles. (Ness 1999; Ness 2000) There is considerable evidence that inflammation is an important mechanism for carcinogenesis (Coussens and Werb 2002; Grivennikov 2010). Alternative plausible mechanisms of carcinogenicity include talc induced oxidative stress (Buz’Zard 2007; Saed 2017; Fletcher 2018), and genotoxicity (Shukla 2009).

The evidence that commercial cosmetic talcum powder products have been shown to contain asbestos, fibrous talc, and heavy metals (Blount 1991; Paoletti 1984; Longo et al 2017, Crowley report 2018) provides a reasonable basis for hypothesizing that these

chemicals may contribute to the carcinogenicity of the talcum powder products. Asbestos is a well-known carcinogen, as are chromium and nickel compounds. It is plausible that any of these, in contact with the ovaries, can be carcinogenic.

The fact that there are credible biologically plausible mechanisms by which talcum powder products can reach the upper genital tract causing an inflammatory response, along with the presence of asbestos fibres and other carcinogens is an important consideration in support of my opinion that the genital use of talcum powder products can cause ovarian cancer.

Aspects of lesser importance in my weighting

Cessation of exposure. It is rare that there is valid evidence available to assess the impact of cessation of exposure in an observational study. In the studies on talcum powder and ovarian cancer, there is no evidence one way or the other concerning the effect of cessation of exposure. This aspect is not applicable and I place almost no weight on it.

Specificity of the association. This aspect is premised on the notion that an agent-disease association is more likely to reflect a causal association if the agent is not also associated with other diseases. In the 1960's, this seemed like a reasonable argument. In light of evidence from the past 60 years, this argument is no longer made and this aspect has fallen out of usage with the demonstration that some agents can indeed provoke multiple different pathologies. Examples include cigarette smoking, ionizing radiation and asbestos fibers.

So, I do not place much stock in this aspect. However, if I did, I would have to say that genital exposure to talc is associated with ovarian cancer and no other morbidity, which supports the 'specificity' of the relationship."

Analogy

Hill argued that if the agent is similar to another agent that has been shown to be a cause of the disease, then the agent under investigation is more likely to be a cause. The fact that exposure to asbestos fibers can cause cancers in lung, larynx mesothelial tissue and ovaries (IARC 2012) can indicate that, by analogy, talc, which is similar in some respects, might be

able to induce carcinogenesis. Thus, there is an argument for an analogy between talc and asbestos. While this aspect supports causality in Hill's framework, I consider it much less important an aspect than the ones listed above.

Coherence with other types of knowledge: Coherence with other knowledge can encompass a multitude of possibilities. This aspect is both vague and very open-ended, with no real operational instruction on how to use it. Hill gave an example in his paper, but the example was only applicable to tobacco and lung cancer. This is an aspect that, if it can be demonstrated, can enhance the likelihood of causality, but its absence cannot detract from causality. I don't consider it to have much weight in this context.

9. Contrast with IARC Monograph and other reviews

The 2006 IARC Monograph meeting, which I chaired, found that a causal relationship was "possible" between perineal talc powder exposure and ovarian cancer. I concurred with that evaluation.

It is now my professional opinion, based on the totality of the evidence that, to a reasonable degree of scientific certainty, the causal relationship between perineal talc powder exposure and ovarian cancer is "probable. "

What has changed in the years since the IARC review?

The RR estimates in Table 2 are remarkably consistent in showing a highly statistically significant excess risk. The number of published study results and scientific literature addressing the epidemiology, toxicology, molecular biology, and mechanistic studies has increased since 2006, and the evidence of excess risk has been consistently demonstrated across the past three decades.

The various possible biases that are on the table remain substantially similar to the ones that were considered by the IARC panel. At the time, we were not convinced that the apparent excess risk could be explained by those potential biases or confounding. As stated above, my review of the relevant studies and potential biases has led me to conclude that bias does not explain the consistent increased risks seen across the credible studies.

There is important new information with regard to the issue of dose-response. Contrary to the impression that the IARC panel had of a total absence of dose-response, and even a possible trend in the opposite direction, the results of three recent publications, Terry 2013 and Schildkraut 2016, using cumulative exposure metrics, and Wu 2015 using duration of exposure, all demonstrate a clear compatibility with a dose-response relationship. The recent meta-analysis of Berge 2018 supports the presence of dose-response in both duration and frequency of use. The most convincing of these is the Terry 2013 pooled analysis, which assembled a larger dataset than all other attempts to assess dose-response combined. Clearly, earlier reviews could not have integrated the results from these recent studies.

It is my opinion, based upon the above the data, there is evidence of a dose-response relationship. Penninkilampi 2018 has recently expressed a similar opinion.

10. Conclusion

The totality of evidence demonstrates that perineal or genital use of talcum powder products is associated with ovarian cancer. Based on contemporary data, my estimated RR between ever perineal use of talc powder products and ovarian cancer (all types combined) is 1.28 (95%CI 1.19-1.38). The body of epidemiologic evidence is remarkably consistent in demonstrating an excess risk. The evidence summarized in Table 6 is compatible with the presence of a dose-response relationship between cumulative exposure to talcum powder products and ovarian cancer. There are various potential sources of bias in these studies, some of which could have inflated the true RR estimate and some of which would have deflated the true RR estimate. Apart from random measurement error, which is inevitable in such studies and which tends to deflate the RR estimates, there is no certainty that the other potential biases were in fact operative and to what degree. It is my opinion, however, that neither bias nor confounding explains the consistent positive association seen across studies. Additionally, there are biologically plausible mechanisms by which talcum powder products can cause ovarian cancer.

Based on the totality of the evidence, it is my opinion, to a reasonable degree of scientific certainty, that the perineal use of talcum powder products can cause ovarian cancer. Given the seriousness of ovarian cancer and its associated morbidity, this causal risk represents an important public health issue.

11. Tables

Table 1. Steps in my evaluation of general causation between talcum powder product use and ovarian cancer

1. Identify all epidemiology study papers that present results on talc and Ovarian Cancer.
2. Extract all RR results from every paper into a database.
3. Determine which of the papers and results present truly independent relevant results.
4. Extract from each study the RR for Ever/Never use of talc in the genital area in relation to OC risk.
5. Conduct a Meta-analysis.
6. Examine the evidence about a possible dose-response relationship.
7. Consider issues of bias, confounding and other sources of error in the various studies.
8. Consider relevant opinion pieces, review articles, and agency reports.
9. Consider opinions from experts regarding possible biological mechanisms.
10. Consider all relevant aspects of association to infer causation.
11. Write report.

Table 2. Relative risk estimates between ever regular use of talcum powders products[1] in the perineal area and ovarian cancer[2], from various studies used in the Main Meta-analysis or in one or more of seven sensitivity analyses

Author	Included in Main meta-analysis	All tumours			
		Number exposed cases	RR[3]	95% CI[4]	
Booth 1989	⍰	141	1.29	0.92	1.80
Chen, 1992	⍰	7	3.9	0.91	10.6
Cook 1997	⍰	159	1.5	1.1	2.0
Cramer 1982	⍰	60	1.55	0.98	2.47
Cramer 2016		642	1.33	1.16	1.52
Gates 2008		57	1.24	0.83	1.83
Gates 2010	⍰	231[5]	1.06	0.89	1.28
Godard 1998	⍰	18	2.49	0.94	6.58
Gonzalez 2016	⍰	17	0.73	0.44	1.2
Harlow 1989	⍰	49	1.1	0.7	2.1
Harlow 1992	⍰	114	1.5	1.0	2.1
Hartge 1983	⍰	7	2.5	0.7	10.0

Author	Included in Main meta-analysis	All tumours			
		Number exposed cases	RR[3]	95% CI[4]	
Houghton 2014	✓	181	1.12	0.92	1.36
Mills 2004	✓	106	1.37	1.02	1.85
Ness 2000	✓	161	1.5	1.1	2.0
Purdie 1995	✓	467	1.27	1.04	1.54
Rosenblatt 1992	✓	22	1.7	0.7	3.9
Schildkraut 2016 A[5]	✓	248	1.44	1.11	1.86
Schildkraut 2016 B[5]		128	1.19	0.87	1.63
Shushan 1996		21	1.97	1.06	3.66
Terry 2013	✓	2600	1.24	1.15	1.33
Terry-AUS 2013		705	1.13	0.92	1.38
Terry-DOV 2013		272	1.13	0.93	1.36
Terry-HAW 2013		74	0.99	0.70	1.41
Terry-HOP 2013		194	1.34	1.07	1.67
Terry-NCO 2013		195	1.37	1.05	1.80
Terry-NEC 2013		755	1.28	1.12	1.47
Terry-SON 2013		197	1.35	1.03	1.76

Author	Included in Main meta-analysis	All tumours			
		Number exposed cases	RR[3]	95% CI[4]	
Terry-USC 2013		208	1.36	1.06	1.74
Tzonou 1993	?	6	1.05	0.28	3.98
Whittemore 1988	?	67	1.36	0.91	2.04
Wong 1999	?	157	1.0	0.8	1.3
Wu 2015	?	701	1.46	1.27	1.69

1. In all of these studies the exposure was defined as ever use of powder in the perineal area. In most studies it was further explicitly indicated that the use was regular.
2. In this table we report the result for all types of ovarian cancer combined. With the exception of the Harlow 1989 study that was restricted to borderline tumours, we have assumed that all studies included both borderline and invasive tumours, although this was not always clear in the publications.
3. RR or OR.
4. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.
5. Estimated based on Table 1 of Gates 2010.
6. The Schildkraut 2016 case-control study presented two sets of results that both have some legitimacy for the present purpose. Schildkraut 2016A shows the results for all subjects who were interviewed in the study from 2010-2015. Schildkraut2016B shows the results for those subjects who were interviewed before 2014, and who, according to the authors, were not susceptible to having been tainted by publicity from a class action suit.

Table 3. Main meta-analysis and sensitivity analyses conducted on the association between ever regular use of talcum powder products in the perineal area and ovarian cancer (all types combined).

		RR-estimate				Heterogeneity	
Studies in meta-analysis	N*	Meta-RR	95% CI		p-value	I^2	p-value
Main Meta-Analysis - list in Figure 1 Forest plot	21	1.28	1.19	1.38	0.00	32.9	0.07
Sensitivity analyses							
Substitute Gates 2008 for Gates 2010	21	1.30	1.21	1.40	0.00	22.9	0.16
Substitute Schildkraut B for Schildkraut A	21	1.27	1.17	1.37	0.00	30.8	0.08
Add Shushan	22	1.29	1.19	1.39	0.00	33.8	0.06
Substitute List A** for Terry	27	1.27	1.19	1.35	0.00	26.2	0.10
Substitute List A for Terry and Gates 2008 for Gates 2010	27	1.29	1.21	1.37	0.00	16.6	0.22
Substitute List A for Terry and Schildkraut B for Schildkraut A	27	1.26	1.18	1.34	0.00	24.5	0.12
Substitute List A for Terry and add Shushan	28	1.28	1.20	1.36	0.00	27.4	0.09

*N: Number of RRs that went into the meta-analysis. This is not synonymous with the number of studies because some RRs (e.g. Terry 2013, Cramer 2016) embody multiple studies.

**List A studies: Cramer 2016; Wu 2015; Terry-Aus 2013; Terry-DOV 2013; Terry-Haw 2013; Terry-HOP 2013; Terry-NCO 2013; Terry SON 2013

Table 4. Comparison of results of three contemporaneous and independent meta-analyses of the association between ever regular use of talcum powder products in the perineal area and ovarian cancer.

Meta-analysis author	N*	Meta-RR	95% CI	Heterogeneity p-value
Siemiatycki 2018	21	1.28	1.19-1.38	0.07
Berge 2018	27	1.22	1.13-1.30	0.02
Penninkilompi 2018	26	1.35	1.24-1.39	0.31

* Number of published RR estimates that went into the meta-analysis. This does not necessarily correspond to the number of studies, since, for example, the Terry 2013 pooled estimate used in the Siemiatycki meta-analysis embodied 10 studies.

Table 5. Relative risk estimates between ever regular use of talcum powder products on sanitary napkins and ovarian cancer, and results of meta-analysis.

Author	**Number exposed cases**	**RR[1]**	**95% CI[2]**	
Chang 1997	51	1.26	0.81	1.96
Cook 1997	38	0.9	0.5	1.5
Cramer 1999	20	1.45	0.68	3.09
Gertig 2000	32	0.89	0.61	1.28
Harlow 1989	8	2.6	0.9	22.4[2]
Harlow 1992	9	1.1	0.4	2.8
Houghton 2014	93	0.95	0.76	1.20
Ness 2000	77	1.6	1.1	2.3
Rosenblatt 1992	21	4.8	1.3	17.8
Rosenblatt 2011	55	0.82	0.58	1.16
Whittemore 1988	5	0.62	0.21	1.80
Wong 1999	13	0.9	0.4	2.0
Meta-analysis		**1.08**	**0.89**	**1.31**
		p-value for heterogeneity = 0.09		

1. RR or OR.
2. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.

Table 6. Relative risk estimates between subgroups defined by cumulative exposure measures[1] and ovarian cancer[2], from various studies.

Author	Cumulative applications[3]	Number exposed cases	RR[4]	95% C.I.	
Cook 1997[4]	< 2000	20	1.8	0.9	3.5
	2001-5000	24	1.6	0.9	2.9
	5001-10000	21	1.2	0.6	2.4
	>10000	28	1.8	0.9	3.4
Harlow 1992	<1000	18	1.3	0.7	2.7
	1000-10000	54	1.5	0.9	2.4
	>10000	42	1.8	1.0	3.0
Mills 2004	Quartile 1	18	1.0	0.6	1.8
	Quartile 2	28	1.8	1.1	3.0
	Quartile 3	34	1.7	1.1	2.7
	Quartile 4	20	1.1	0.6	1.8
	10000+	18	0.87	0.48	1.57
Schildkraut 2016	≤3600	92	1.16	0.83	1.63
	>3600	152	1.67	1.23	2.26
Terry 2013[5]	Quartile 1	534	1.14	1.00	1.31
	Quartile 2	541	1.23	1.08	1.41
	Quartile 3	542	1.22	1.07	1.40
	Quartile 4	586	1.32	1.16	1.52

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a cumulative measure. All of these were case control studies.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. For the Cook study the metric was the number of days on which the woman had ever applied the powder. For the other studies the metric is based on an estimate of the total number of applications.

4. RR or OR.
5. This study was based on a pooling of studies from 8 teams. Two of the teams (Cramer 2016 and Rosenblatt 2011) published separate analyses of risk by cumulative number of applications. But these are not shown here because they are rendered redundant by the Terry 2013 pooled results.

Table 7. Relative risk estimates between subgroups defined by duration of use[1] and ovarian cancer[2], from various studies.

Author	Duration of use	Number exposed cases	RR[4]	95% C.I.	
Chang 1997	<30	60	1.7	1.1	2.6
	30-40	71	1.4	1.0	2.2
	>40	41	0.9	0.5	1.4
Cramer 1999	<20 years	55	1.9	1.2	3.0
	20-30 years	32	1.3	0.8	2.3
	>30 years	59	1.4	0.9	2.3
Cramer 2016	< 8 years of use	133	1.31	1.03	1.68
	8-19 years of use	126	1.31	1.02	1.68
	20-35 years of use	147	1.35	1.07	1.70
	>35 years of use	129	1.33	1.03	1.71
Harlow 1992	<10 years	14	1.2	0.5	2.6
	10-29 years	49	1.6	1.0	2.7
	> 30 years	51	1.6	1.0	2.7
Houghton 2014	<9 years	135	1.09	0.88	1.36
	10+ years	97	1.02	0.80	1.30
Ness 2000	<1 year	17	2.0	1.0	4.0
	1-4 years	76	1.6	1.1	2.3
	5-9 years	40	1.1	0.8	1.9
	>10 years	233	1.2	1.0	1.5
Mills 2004	<3 years	18	1.0	0.6	1.8
	4-12 years	32	1.9	1.2	3.0
	13-30 years	29	1.5	0.9	2.3
	>30 years	21	1.2	0.7	2.1

Author	Duration of use	Number exposed cases	RR[4]	95% C.I.	
Rosenblatt 2011	1-9 years	33	1.39	0.85	2.28
	10-19 years	29	1.46	0.87	2.45
	20-34 years	30	1.28	0.78	2.10
	35+ years	19	0.91	0.51	1.62
Schildkraut 2016	≤20 years	101	1.33	0.95	1.86
	>20 years	144	1.52	1.11	2.07
Whittemore 1988	1-9 years	34	1.6	1.0	2.6
	10+	50	1.1	0.7	1.7
Wong 1999	1-9 years	39	0.9	0.6	1.5
	10-19 years	49	1.4	0.9	2.2
	>20 years	101	0.9	0.6	1.2
Wu 2015	Per 5 years of exposure	1273	1.14	1.09	1.20

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a measure of duration.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
4. RR or OR.

Table 8. Relative risk estimates between subgroups defined by measures of frequency of use[1] and ovarian cancer[2], from various studies.

Author	**Frequency of use**	**Number exposed cases**	**RR[4]**	**95% C.I.**	
Booth 1989	Rarely	6	0.9	0.3	2.4
	Monthly	7	0.7	0.3	1.8
	Weekly	57	2.0	1.3	3.4
	Daily	71	1.3	0.8	1.9
Chang 1997	<10 per month	76	1.8	1.2	2.7
	10-25 per month	54	1.1	0.7	1.7
	Per 10 applications per month		0.9	0.7	1.1
Cramer 1999	<30 per month	64	2.2	1.4	3.6
	30-39 per month	59	1.7	0.8	1.8
	≥40 per month	23	1.7	0.8	3.1
Cramer 2016	1-7 days per month	220	1.17	0.96	1.44
	8-29 days per month	110	1.37	1.05	1.78
	>30 days per month	205	1.46	1.20	1.78
Gates 2008	<1 per week	18	0.98	0.54	1.79
	1-6 per week	22	1.01	0.57	1.79
	Daily	35	1.44	0.88	2.37
Harlow 1992	<5 per month	32	1.5	0.8	2.7
	5-29 per month	24	1.2	0.6	2.2
	≥30 per month	58	1.8	1.1	3.0

Author	Frequency of use	Number exposed cases	RR[4]	95% C.I.	
Mills 2004	<1 per week	34	1.3	0.9	2.1
	1-3 per week	31	1.6	0.7	1.8
	4-7 per week	41	1.7	1.1	2.6
Schildkraut 2016	<Daily	88	1.12	0.80	1.58
	Daily	158	1.71	1.26	2.33
Whittemore 1988	1-20 per month	41	1.3	0.8	2.0
	>20 per month	44	1.5	0.9	2.2

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a measure of frequency of use.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
4. RR or OR

Table 9. Relative risk estimates between ever regular use of talcum powder products[1] in the perineal area and invasive serous ovarian cancer, from various studies.

Author	Number exposed cases	RR[2]	95% CI[3]	
Cook 1997	71	1.7	1.1	2.5
Gates 2010	131[4]	1.06	0.84	1.35
Harlow 1992	60	1.4	0.9	2.2
Houghton 2014	105	1.13	0.84	1.51
Mills 2004	42	1.77	1.12	2.81
Schildkraut 2016	165	1.38	1.03	1.85
Terry 2013	1197	1.24	1.13	1.35
Wong 1999	136	1.2	0.7	2.1
Meta-analysis		**1.25**	**1.15**	**1.36**
			p-value for heterogeneity 0.06	

1. In all of these studies the exposure was defined as ever use of powder in the perineal area. In most studies it was further explicitly indicated that the use was regular.
2. RR or OR.
3. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.
4. Estimated based on Table 1 of Gates 2010.

Table 10. Some major misconceptions in reviewing evidence on talc and ovarian cancer

1. Cohort studies are more valid and informative than case-control studies.
2. Hospital-based case-control studies are more valid and informative than the population-based case-control studies.
3. Counting the number of "statistically significant" results is a valid way of assessing the consistency of results among multiple studies.
4. If a product has been used for a long time, it must be safe
5. You cannot prove causality with an RR less than 2.0.
6. Government agencies provide a reliable up-to-date source of scientific information.
7. A biological mechanism must be proven before we can establish causality
8. Bradford-Hill "aspects" represent a recipe list of necessary ingredients.

Table 11. Selected examples of some of the recognized causal associations that have RR less than 2.0

Agent	**Disease**	**Approximate RR**
Urban air pollution	Lung cancer	1.09[1]
Trichloroethylene	Kidney cancer	1.32[2]
Diesel engine emissions	Lung cancer	1.42[3]
Benzene	Leukemia	1.72[4]
Domestic radon gas	Lung cancer	1.29[5]
Second hand cigarette smoke	Lung cancer	1.64
Intermittent intense sun exposure	Melanoma of the skin	1.61[6]
Estrogen-progestin menopausal therapy	Breast cancer	1.59[7]

[1] Hamra GB, Guha N, Cohen A, et al (2014). Outdoor Particulate Matter Exposure and Lung Cancer: A Systematic Review and Meta-Analysis, *Environ Health Perspect* 122:906-911.
[2] Karami S, Lan Q, Rothman N, et al (2012). Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. *Occupational and Environmental Medicine* 69:858-867.
[3] Mahjub H, Sadri G (2006). Meta-analysis of case-referent studies of specific environmental or occupational pollutants on lung cancer. *Indian Journal of Cancer* 43(4):169-173.
[4] Khalade A, Jaakkola MS, Pukkala E, Jaakkola JJ (2010). Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis. *Environmental Health* 9(31):1-8.
[5] Zhang Z-L, Sun J, Dong J-Y, et al (2012). Residential Radon and Lung Cancer Risk: An Updated Meta-analysis of Case-control Studies. *Asian Pac J Cancer Prev* 13:2459-2465.
[6] Gandini S, Sera F, Cattaruzza MS, et al (2004). Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *European Journal of Cancer* 41:45-60.
[7] Kim S, Ko Y, Lee HJ, Lim J (2018). Menopausal hormone therapy and the risk of breast cancer by histological type and race: a meta-analysis of randomized controlled trials and cohort studies. *Breast Cancer Research and Treatment* 170(3):667-675.

Cigarette smoking	Cardiovascular disease	1.6[8]
Physically inactive (compared with physically active) [9]	Hypertension	1.19
	Diabetes	1.12
Low fruit and vegetable diet	Cardiovascular disease	1.09[10]

[8] Doll R, Peto R, Boreham J, Sutherland I (2004). Mortality in relation to smoking: 50 years' observations on British male doctors, *British Medical Journal*, 328(7455):1519.
[9] Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs, Jr DR, Liu K (2003). Cardiorespiratory Fitness in Young Adulthood and the Development of Cardiovascular Disease Risk Factors. *JAMA*, 290(23):3092–3100
[10] Aune D, Giovannucci E, Boffetta P, Fadnes L, Keum N, Norat T, Greenwood D, Riboli E, Vatten L, Tonstad S (2017). Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality – a systematic review and dose-response meta-analysis of prospective studies, International Journal of Epidemiology 43(3):1029-1056. (This RR estimate is computed from the reciprocal of the High fruit and vegetable variable that was reported by the authors. That is, 1/0.92).

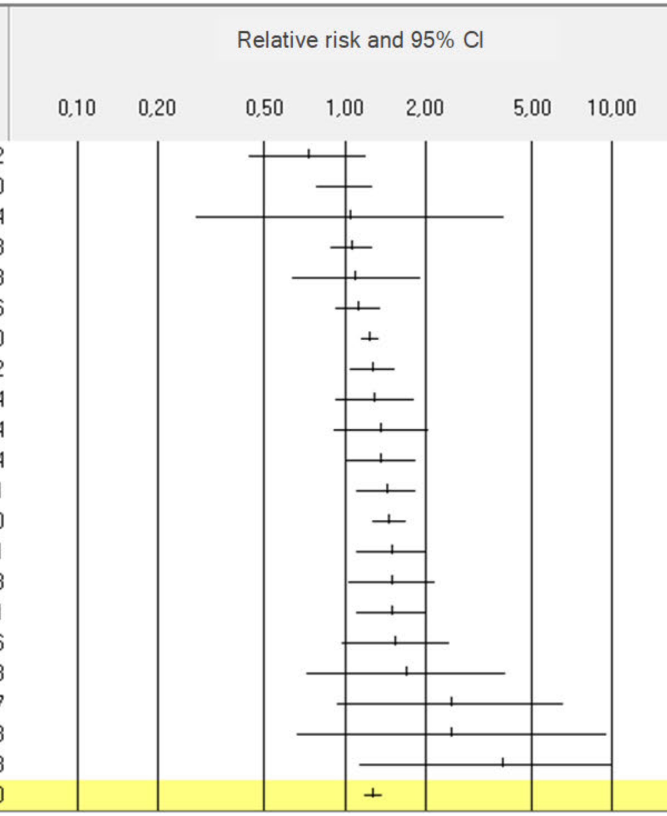
Table 12. Bradford Hill aspects in relation to perineal talc exposure and ovarian cancer

Aspect	**Brief comment**	**Weight in evaluating causality**
Strength of the association	There are stronger associations and there are weaker associations	High
Dose response relationship	Reasonably clear increase in risk with increasing exposure	High
Consideration of alternative explanations – absence of bias	Yes considered, and none is compelling	High
Replication of the findings	Very strong, almost all studies support association	High
Temporal relationship	Exposure preceded disease in all studies	Moderate
Biological plausibility	There are plausible mechanisms	Moderate
Cessation of exposure	Not applicable.	Less
Specificity of the association	Yes, talc is not associated with a multitude of diseases	Less
Coherence with other knowledge	Could be similar to asbestos carcinogenicity	Less
Analogy		Less

12. Figures

Figure 1. Meta-analysis of relative risk of ovarian cancer (all types combined) among women who regularly used talc powder in the perineal area, based on all informative studies, studies ordered by magnitude of RR.

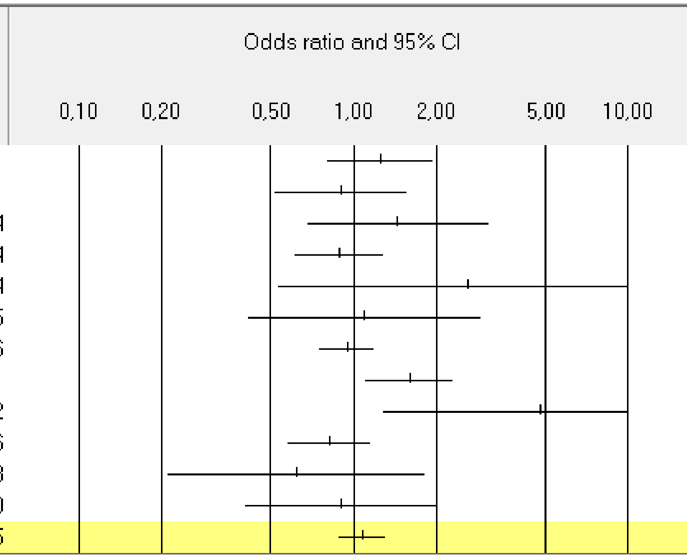
Model	Study name	Statistics for each study				Weight (Random)
		Risk ratio	Lower limit	Upper limit	p-Value	Relative weight
	Gonzalez 2016	0,73	0,44	1,21	0,22	2,05
	Wong 1999	1,00	0,78	1,27	1,00	6,50
	Tzonou 1993	1,05	0,28	3,96	0,94	0,32
	Gates 2010	1,06	0,88	1,27	0,53	9,17
	Harlow 1989	1,10	0,64	1,91	0,73	1,74
	Houghton 2014	1,12	0,92	1,36	0,26	8,48
	Terry 2013	1,24	1,15	1,33	0,00	16,37
	Purdie 1995	1,27	1,04	1,55	0,02	8,43
	Booth 1989	1,29	0,92	1,80	0,14	4,05
	Whittemore 1988	1,36	0,91	2,04	0,14	3,00
	Mills 2004	1,37	1,02	1,85	0,04	4,87
	Schildkraut 2016 A	1,44	1,11	1,86	0,01	5,98
	Wu 2015	1,46	1,27	1,68	0,00	11,46
	Cook 1997	1,50	1,11	2,02	0,01	4,84
	Harlow 1992	1,50	1,04	2,17	0,03	3,45
	Ness 2000	1,50	1,11	2,02	0,01	4,84
	Cramer 1982	1,55	0,98	2,46	0,06	2,37
	Rosenblatt 1992	1,70	0,72	4,01	0,23	0,75
	Godard 1998	2,49	0,94	6,59	0,07	0,59
	Hartge 1983	2,50	0,66	9,45	0,18	0,32
	Chen, 1992	3,90	1,14	13,31	0,03	0,38
Random		1,28	1,19	1,38	0,00	



Model	Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	21	1,264	1,204	1,327	9,474	0,000	29,813	20	0,073	32,916	0,008	0,008	0,000	0,088
Random effects	21	1,280	1,186	1,381	6,364	0,000								

Figure 2. Meta-analysis of relative risk of ovarian cancer (all types combined) among women who regularly used talcum powder products on sanitary napkins, based on all informative studies.

Model	Study name	Statistics for each study: Odds ratio	Lower limit	Upper limit	p-Value	Weight (Random): Relative weight
	Chang 1997	1,26	0,81	1,96	0,31	11,14
	Cook 1997	0,90	0,52	1,56	0,71	8,47
	Cramer 1999	1,45	0,68	3,09	0,34	5,26
	Gertig 2000	0,89	0,61	1,29	0,54	13,44
	Harlow 1989	2,60	0,53	12,74	0,24	1,41
	Harlow 1992	1,10	0,42	2,91	0,85	3,45
	Houghton 2014	0,95	0,76	1,19	0,66	19,32
	Ness 2000	1,60	1,11	2,31	0,01	13,50
	Rosenblatt 1992	4,80	1,30	17,76	0,02	2,03
	Rosenblatt 2011	0,82	0,58	1,16	0,26	14,32
	Whittemore 1988	0,62	0,21	1,82	0,38	2,90
	Wong 1999	0,90	0,40	2,01	0,80	4,76
Random		1,08	0,89	1,31	0,45	



Model	Number Studies	Effect size and 95% interval: Point estimate	Lower limit	Upper limit	Test of null (2-Tail): Z-value	P-value	Heterogeneity: Q-value	df (Q)	P-value	I-squared	Tau-squared: Tau Squared	Standard Error	Variance	Tau
Fixed	12	1,041	0,911	1,189	0,591	0,554	17,614	11	0,091	37,551	0,037	0,045	0,002	0,193
Random effects	12	1,078	0,888	1,309	0,763	0,445								

Figure 3. Meta-analysis of relative risk of invasive serous ovarian cancer among women who regularly used talcum powder products in the perineal area, based on all informative studies

Model	Study name	Statistics for each study				Relative risk and 95% CI	Weight (Random)
		Risk ratio	Lower limit	Upper limit	p-Value	0,10 0,20 0,50 1,00 2,00 5,00 10,00	Relative weight
	Cook 1997	1,70	1,13	2,56	0,01		4,13
	Gates 2010	1,06	0,84	1,34	0,63		11,79
	Harlow 1992	1,40	0,90	2,19	0,14		3,49
	Houghton 2014	1,13	0,84	1,52	0,41		7,90
	Mills 2004	1,77	1,12	2,80	0,01		3,30
	Schildkraut 2016	1,38	1,03	1,85	0,03		7,92
	Terry 2013	1,24	1,13	1,36	0,00		59,13
	Wong 1999	1,20	0,69	2,08	0,52		2,33
Random		1,25	1,15	1,36	0,00		

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared			
Fixed	8	1,250	1,161	1,345	5,963	0,000	7,401	7	0,388	5,422	0,001	0,011	0,000	0,033
Random effects	8	1,254	1,152	1,364	5,249	0,000								

13. Appendix A

Appendix Table A1. Papers that contain some results on the association between exposure to perineal talc and ovarian cancer, and whether the paper was included in my meta-analyses of the binary Ever/Never exposed variable

Author	Included/excluded	Reasons for exclusion
Booth 1989	Core Inclusion	
Chang 1997	Core Inclusion	
Chen 1992	Core Inclusion	
Cook 1997	Core Inclusion	
Cramer 1982	Core Inclusion	
Cramer 1995	Excluded	Included in Terry 2013 and in Cramer 2016
Cramer 1999	Excluded	Included in Terry 2013 and in Cramer 2016
Cramer 2005	Excluded	Included in Terry 2013 and in Cramer 2016
Cramer 2016	Excluded when Terry 2013 is included	Considerable overlap between this and the Terry 2013 NEC component
Eltabbakh 1998	Excluded	Cases were peritoneal cancer and controls were ovarian cancer
Gates 2008[2-]	Included in one sensitivity analysis	Overlap with Gates 2010

Author	Included/excluded	Reasons for exclusion
Gates 2010[2]	Included in all analyses except one sensitivity analysis	This may be a more complete analysis than Gates 2008, but the degree of overlap is unclear.
Gertig 2000	Excluded	Subsumed in Gates 2008 and Gates 2010
Godard 1998	Core inclusion	
Gonzalez 2016	Core inclusion	
Green 1997	Excluded	This appears to be an analysis of a subset of the subjects in Purdie 1995
Hankinson 1993	Excluded	Numerical results were not presented.
Harlow 1989	Core inclusion	
Harlow 1992	Core inclusion	
Hartge 1983	Core inclusion	
Houghton 2014	Core inclusion	
Jordan 2007	Excluded	Benign tumours only
Kurta 2012	Excluded	Included in Terry 2013
Langseth 2004	Excluded	Not based on perineal application of cosmetic powder.
Lo-Ciganic 2012	Excluded	Same study as Kurta 2012 and included in Terry 2013.
Merrit 2008	Excluded	Included in Terry 2013

Author	**Included/excluded**	**Reasons for exclusion**
Mills 2004	Core inclusion	
Moorman 2009	Excluded	Included in Terry 2013
Pike 2004	Excluded	Included in Terry 2013
Purdie 1995	Core inclusion	
Ness 2000	Core inclusion	
Rosenblatt 1992	Core inclusion	
Rosenblatt 2011	Core inclusion	
Schildkraut 2016	Core inclusion	
Shushan 1996	Included in sensitivity analysis	Unclear on how they obtained data on talc exposure or what the route of exposure was
Terry 2013	Included in Main analysis, but replaced by component studies in sensitivity analyses	
Tzonou 1983	Core inclusion	
Whittemore 1988	Core inclusion	
Wong 1999	Core inclusion	
Wu 2015	Core inclusion	

Appendix Table A2. Some administrative and contextual information on the studies used in the following tables

Author	Study location	Years of case ascertainment/ follow-up[1]	Type of study
Booth 1989	London, Oxford UK	1978-1983	Case-control; Hospital controls
Chen 1992	Beijing Cancer Registry	1984-1986	Case-control; Population controls
Cook 1997	Washington State	1986-1988	Case-control; Population controls
Cramer 1982	Boston	1978-1981	Case-control; Population controls
Cramer 2016	New England	1992-2008	Case-control; Population controls
Gates 2008[2-]	USA – NHS study	1976-2004	Case-control nested in Cohort (US nurses)
Gates 2010[2]	USA – pooled 2 cohorts of nurses NHS and NHSII	1976-2004 1989-2005	Cohort (US Nurses)
Godard 1998	Montreal, Canada	1995-1996	Case-control; Population controls
Gonzalez 2016	Puerto Rico and 11 States USA	2003-2014	Cohort
Harlow 1989	Washington State	1980-1985	Case-control; Population controls
Harlow 1992	Boston	1984-1987	Case-control; Population controls

Author	Study location	Years of case ascertainment/ follow-up[1]	Type of study
Hartge 1983	Washington, DC	1974-77	Case-control; Population controls
Houghton 2014	USA	1993-2012	Cohort (WHI)
Mills 2004	California	2000-2001	Case-control; Population controls
Ness 2000	Pennsylvania, New Jersey, Delaware	1994-1998	Case-control; Population controls
Purdie 1995	Australia	1990-1993	Case-control; Population controls
Rosenblatt 1992	Baltimore	1981-1985	Case-control; Hospital controls
Schildkraut 2016	USA	2010-2015	Case-control; Population controls
Shushan 1996	Israel	1990-1993	Case-control Population controls
Terry 2013	Pooled 8 studies: USA & Australia	1984-2008	Case-control; Population controls
Terry-AUS 2013	Australia	2002-2006	Case-control Population controls
Terry – DOV[3] 2013	Washington State	2002-2009	Case-control Population controls
Terry – HAW 2013	Hawaii	1993-2008	Case-control Population controls

Author	Study location	Years of case ascertainment/ follow-up[1]	Type of study
Terry – HOP 2013	Pennsylvania, Ohio, Western NY State	2003-2008	Case-control Population controls
Terry – NCO 2013	North Carolina	1999-2008	Case-control Population controls
Terry – NEC 2013	Massachusetts, New Hampshire	1992-2006	Case-control Population controls
Terry – SON 2013	Southern Ontario	1989-1992	Case-control Population controls
Terry – USC 2013	Los Angeles County	1992-1998	Case-control Population controls
Tzonou 1983	Athens	1989-1991	Case-control; Controls – hospital visitors
Whittemore 1988	San Francisco	1983-1985	Case-control; Hospital & population controls
Wong 1999	Buffalo	1982-1992	Case-control; Hospital controls
Wu 2015	Los Angeles County	1992-2008	Case-control; Population controls

1. Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
2. The Gates 2008 and Gates 2010 papers are both derived from the U.S. Nurses Cohort. The latter represent results for all cases diagnosed up to 2006 and analysed in the cohort framework. The former represents results for a sub-set of cases that were selected for a nested c-c analysis. The number of exposed cases was not given in the Gates 2010 paper.
3. Terry – DOV 2013: the information in Terry 2013 is updated information included in Rosenblatt 2011.

Appendix Table A3. Covariates used in the analyses and exposure variables in the studies used in the following tables.

Author	Exposure variable selected	Covariates used in analysis
Booth 1989	At least monthly use	Since the authors did not present results for “ever” exposed, I calculated the OR from crude numbers in their tables. Therefore the OR presented is a crude one. However, results presented in Table 7 adjusted for age and social class
Chen 1992	Dusting perineum or lower abdomen > 3 months	Education
Cook 1997	Lifetime perineal application	Age
Cramer 1982	Any use as dusting powder and/or on sanitary napkins	Parity; menopausal status
Cramer 2016	Any talc use	Age; study center (MA, NH); BMI; primary relative with breast or ovarian cancer; parity; OC use; tubal ligation
Gates 2008[1-]	Regular genital talc use (1 per week or more)	Age; OC[2] use; parity; BMI; post-menopausal hormone use
Gates 2010[1]	Regular genital talc use (1 per week or more)	Age; BMI; physical activity; smoking; family history of breast or ovarian ca; OC use; tubal ligation; hysterectomy; age menopause; estrogen use
Godard 1998	Ever use of talc on perineum	Age; reproductive factors; OC use; tubal ligation; alcohol use; breast and abdominal surgery
Gonzalez 2016	Talc use in the past 12 months	Race; body mass index; parity; duration of oral contraceptive use; baseline menopause status; and patency

Author	Exposure variable selected	Covariates used in analysis
Harlow 1989	Any genital talc use	Age; county; parity; OC use
Harlow 1992	Any genital talc use	Age; county; parity; marital status; education; religion; weight; use of sanitary napkins; douching
Hartge 1983	Any genital talc use	Race; age; gravidity
Houghton 2014	Combined use: longest duration of use among the applications to genitals, sanitary napkins and diaphragms	Age; race; OC use; HRT[3] use; family history of ovarian ca; age at last birth; BMI; smoking; tubal ligation; parity
Mills 2004	Ever use of talcum powder in genital area	Age; race/ethnicity; OC use; breast-feeding
Ness 2000	Genital rectal talc use	Age; parity; family history of ovarian ca;
Purdie 1995	Ever used talc in perineal region	Age; parity; duration of OC use; education; BMI; smoking; family history of ovarian ca
Rosenblatt 1992	Ever use of bath talc	Number of live births
Schildkraut 2016	Regular use of talc, cornstarch, baby or deodorising powder – at least once a month for 6 months	Age at diagnosis/interview; study site; education; tubal ligation; parity; BMI duration of OC use first degree family history of breast or ovarian cancer; and interview year
Shushan 1996	Talc use – never, seldom, moderate, a lot	Crude OR

Author	**Exposure variable selected**	**Covariates used in analysis**
Terry 2013 – all components of the pooled analysis	Genital powder use	Age; OC use; parity; BMI; tubal ligation; ethnicity; race; tubal ligation; hysterectomy; breastfeeding
Tzonou 1983	Ever use of talc in perineal region	Age; years of schooling; weight before onset of the disease; age at menarche; menopausal status and age at menopause; parity and age at first birth; tobacco smoking; coffee drinking; consumption of alcoholic beverages; hair dyeing; use of analgesics and tranquilizers/hypnotics
Whittemore 1988	Talcum powder used on any two of perineum, sanitary pads and diaphragm	Age; race; hospital; parity
Wong 1999	Ever use of talc on genital region or thighs	Age; income; education; geographic location; OC use; smoking; family history of ovarian ca; age at menarche; menopausal status; tubal ligation or hysterectomy
Wu 2015	Genital talc use >1 year	Age; race/ethnicity; interviewer; reproductive variables; sociodemographic variables; medical history; hormonal variables; BMI.

1. The Gates 2008 and Gates 2010 papers are both derived from the U.S. Nurses Cohort. The latter represent results for all cases diagnosed up to 2006 and analysed in the cohort framework. The former represents results for a sub-set of cases that were selected for a nested c-c analysis. The number of exposed cases was not given in the Gates 2010 paper.
2. OC: oral contraceptive
3. HRT: hormone replacement therapy

14. Appendix B

Comparison of studies used and results extracted from articles referenced in three different meta-analyses.*

Penninkilampi 2018 Study / RR(95%CI)	Berge 2018 Study / RR(95%CI)	Siemiatycki 2018 Study / RR(95%CI)
Booth 1989 1.30 (0.94-1.80)	***Booth 1989 1.29 (0.92 - 1.80)***	***Booth 1989 1.29 (0.92 - 1.80)***
Chang 1997 1.42 (1.08 – 1.86)	Chang 1997 1.35 (1.03 - 1.76)	
Chen, 1992 3.90 (1.43 – 10.60)	***Chen, 1992 3.90 (0.91 - 10.60)***	***Chen, 1992 3.90 (0.91 - 10.60)***
Cook 1997 1.50 (1.11 – 2.02)	***Cook 1997 1.50 (1.10 - 2.00)***	***Cook 1997 1.50 (1.10 - 2.00)***
Cramer 1982 1.60 (1.21 – 2.12)	***Cramer 1982 1.92 (1.27 - 2.89)***	***Cramer 1982 1.92 (1.27 - 2.89)***
Cramer 2016 1.42 (1.03 – 1.95	Cramer 2016 1.32 (1.14 - 1.50)	Cramer 2016 1.33 (1.16 – 1.52)
		Gates 2008 1.24 (0.83 - 1.83)
	Gates 2010 1.06 (0.89 - 1.28)	***Gates 2010 1.06 (0.89 - 1.28)***
Gertig 2000 1.09 (0.86 – 1.38)		

Penninkilampi 2018 Study / RR(95%CI)	Berge 2018 Study / RR(95%CI)	Siemiatycki 2018 Study / RR(95%CI)
Godard 1998 ***2.49 (0.94 - 6.58)***	***Godard 1998*** ***2.49 (0.94 - 6.58)***	***Godard 1998*** ***2.49 (0.94 - 6.58)***
Gonzalez 2016 ***0.73 (0.44 - 1.20)***	***Gonzalez 2016*** ***0.73 (0.44 - 1.20)***	***Gonzalez 2016*** ***0.73 (0.44 - 1.20)***
	Goodman 2008 0.99 (0.7 - 1.41)	
Green 1997 1.30 (1.06 – 1.60)		
Harlow 1989 1.10 (0.58 – 2.10)	***Harlow 1989*** ***1.10 (0.70 - 2.10)***	***Harlow 1989*** ***1.10 (0.70 – 2.10)***
	Harlow 1992 ***1.50 (1.00 - 2.10)***	***Harlow 1992*** ***1.50 (1.00 – 2.10)***
Hartge 1983 ***2.50 (0.66 – 9.45)***	***Hartge 1983*** ***2.50 (0.70 - 10.00)***	Hartge 1983 0.70 (0.40 - 1.10)
Houghton 2014 ***1.12 (0.92 – 1.36)***	Houghton 2014 1.06 (0.87 - 1.28)	***Houghton 2014*** ***1.12 (0.92 – 1.36)***
Kurta 2012 1.40 (1.16 – 1.69)		
	Lo-Ciganic 2012 1.34 (1.07 - 1.66)	

Penninkilampi 2018 **Study / RR(95%CI)**	**Berge 2018** **Study / RR(95%CI)**	**Siemiatycki 2018** **Study / RR(95%CI)**
Merritt 2008 1.17 (1.01 – 1.36)	Merritt 2008 1.13 (0.92 - 1.38)	
Mills 2004 ***1.37 (1.02 - 1.85)***	***Mills 2004*** ***1.37 (1.02 - 1.85)***	***Mills 2004*** ***1.37 (1.02 - 1.85)***
	Moorman 2009 1.37 (1.05 - 1.8)	
Ness 2000 ***1.50 (1.10 - 2.02)***	***Ness 2000*** ***1.50 (1.10 - 2.00)***	***Ness 2000*** ***1.50 (1.10 - 2.00)***
Purdie 1995 ***1.27 (1.04 - 1.54)***	***Purdie 1995*** ***1.27 (1.04 - 1.54)***	***Purdie 1995*** ***1.27 (1.04 - 1.54)***
Rosenblatt 1992 1.70 (0.72 – 4.01)	***Rosenblatt 1992*** ***1.70 (0.70 - 3.90)***	***Rosenblatt 1992*** ***1.70 (0.70 - 3.90)***
Rosenblatt 2011 1.27 (0.97 – 1.66)	Rosenblatt 2011 1.13 (0.93 - 1.36)	
Schildkraut 2016 ***1.44 (1.11 - 1.86)***	***Schildkraut 2016*** ***1.44 (1.11 - 1.86)***	***Schildkraut 2016 A*** ***1.44 (1.11 - 1.86)***
		Schildkraut 2016 B 1.19 (0.87 - 1.63)
Shushan 1996 2.00 (1.11 – 3.60)		Shushan 1996 1.97 (1.06 – 3.66)

Penninkilampi 2018 Study / RR(95%CI)	Berge 2018 Study / RR(95%CI)	Siemiatycki 2018 Study / RR(95%CI)
		Terry 2013 1.24 (1.15 - 1.33)
Tzonou 1993 ***1.05 (0.28 - 3.96)***	***Tzonou 1993*** ***1.05 (0.28 - 3.98)***	***Tzonou 1993*** ***1.05 (0.28 - 3.98)***
Whittemore 1988 1.40 (0.98 – 2.00)	***Whittemore 1988*** ***1.36 (0.91 - 2.04)***	***Whittemore 1988*** ***1.36 (0.91 - 2.04)***
Wong 1999 0.92 (0.24 – 3.57)	***Wong 1999*** ***1.00 (0.80 - 1.30)***	***Wong 1999*** ***1.00 (0.80 - 1.30)***
Wu 2015 1.32 (1.14 – 1.52)	***Wu 2015*** ***1.46 (1.27 - 1.69)***	***Wu 2015*** ***1.46 (1.27 - 1.69)***

- * When two or three of the meta-analyses extracted the identical results from the source paper, it is indicated with italic characters.

15. Appendix C

Examples of historic discoveries made on the basis of empirical observation of an association, without the existence of a validated biological mechanism of action.

- Jenner (18th century) discovered that smallpox could be prevented by “vaccinating” people. This was based on observation of the effect of exposure to cowpox. He had no idea about viruses or the biology of smallpox. He only knew that the “association” he observed between vaccination and the prevention of smallpox was so strong as to convince him it was causal. Millions of lives were saved as a result.
- Snow (19th century) discovered that cholera was caused by something in the water supply. He did not know what the pathogen was or how it produced the disease, but he showed with sufficient epidemiologic proof that drinking water from a polluted source produced much higher rates than drinking water from a clean source. Despite the ignorance of biological mechanisms, the public health authorities acted on his findings and thereby greatly reduced the incidence of cholera.
- Rheumatic fever and rheumatic heart disease were quite common causes of disease and death, striking relatively young people. For many decades it was recognized that there was an association between infection with the streptococcus bacterium and rheumatic heart disease, but it was not understood how the bacterium could have such an effect. The lack of understanding of the biological mechanisms did not get in the way of prevention of rheumatic heart disease by preventing and treating streptococcus infection.
- In the 1930’s and 1940’s, it was noticed that communities with high natural levels of fluoride in the water had much lower levels of dental caries than communities with low fluoride levels. Additional observational research confirmed the clear causal relationship and this led to extensive use of fluoride in various ways to reduce dental disease. But, all this occurred

before the mechanisms by which fluoride acted on teeth were understood. And, indeed the mechanisms are still not fully understood.

- In the late 1940's and early 1950's, evidence was accumulating that cigarette smokers had higher rates of lung cancer than non-smokers. This "association" was ridiculed at the time, among other reasons, because there was no proven biological mechanism. Attempts to replicate smoking-related lung cancer incidence in laboratory animals were largely unsuccessful. Nor was there a deep understanding of the cellular processes that allow the inhalation of cigarette smoke to culminate in a tumor. Scores of studies later and many decades later, the outlines of a credible biological mechanism began to emerge. The absence of a proven biological mechanism did not hinder the US Surgeon General and other national bodies from concluding that there was a causal link as early as the 1960's.

- Many chemicals have been found to be carcinogenic as a result of epidemiologic studies among workers. Examples of these are asbestos, silica, nickel compounds, chromium compounds, benzene, and others. Some of these discoveries go back to the first half of the 20th century, and, for most of them, many decades passed between the time they were recognized as carcinogens, on the basis of epidemiologic associations, and the elaboration of credible mechanisms of how they induce cancer. (Siemiatycki 2015) Most known carcinogens were first discovered empirically by medical doctors or epidemiologists, usually as part of large data collection activities or just plain astute observation on the part of medical doctors.

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Agenda: NTP Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee Meeting

Annie Yessian Report - Echeverria

Berg v. Johnson & Johnson, Final Jury Instructions

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California State Cosmetics Program from the California Dept of Public Health - Occupational health Branch - Chemicals known or suspected to cause cancer or reproductive toxicity (P-31)

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Cancer Prevention Coalition – November 17, 1994 Citizen's Petition to FDA seeking carcinogenic labelling on all cosmetic talc products

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David Steinberg publications list

David Steinberg signed verification Di Saia, P. J. (2015). Letter to Kathleen A. Frazier. Unpublished letter.

Defense Expert Reports from Blaes Case: DeSesso; Hoel; Di Saia; Muscat; Hopkins

Deposition Exhibit of John Hopkins – 28 (November 5, 2018)

Deposition Exhibit of Julie Pier – 47 (September 13, 2018)

Deposition Transcript of Alice Blount, *Ingham v. Johnson & Johnson, et al*. (April 13, 2018)

Deposition Transcript & Exhibits - Julie Pier, MDL No. 2738 (September 12 – 13, 2018)

Deposition transcript, 10/19/2012 - John Hopkins

Deposition Transcript & Exhibits - John Hopkins, MDL No. 2738 (Aug. 16 – 17, 2018, Oct. 17, 2018, Nov. 5, 2018)

Deposition Transcript & Exhibits - Joshua Muscat, MDL No. 2738 (Sept. 25, 2018)

Deposition Transcript & Exhibits - Linda Loretz, MDL No. 2738 (July 17, 2018, Oct. 1 – 2, 2018)

Deposition Transcript & Exhibits - Robert Glenn, MDL No. 2738 (Oct. 18, 2018)

D. L. Longo, R. C. Young. Cosmetic talc and ovarian cancer (1979)

D. L. Longo, R. C. Young. Letter to the Editor: Cosmetic talc and ovarian cancer (1979)

Educational Report of Thomas Dydek

Excerpts from S. Sharma Deposition

Expert Report of Laura M. Plunkett, PhD, DABT – Oct. 5, 2016

Expert Report of Jack Siemiatycki, MSc, PhD – Oct. 4, 2016

Fair warning TalcDoc 5 - Exhibit 113 (JNJNL91_000022019)

Fair warning TalcDoc 15

FDA Authority Over Cosmetics April 6, 2015

FDA Response to Citizen's Petition re: Docket Numbers 94P-0420 and FDA-2008-P-0309-00001/CP

Federal Register – 81 FR 91722 – Banned Devices – Powdered Gloves

Fox v. Johnson & Johnson, Trial Transcript

Godleski, J. J. (2015). Letter to R. Allen Smith, Jr. Unpublished letter.

John J. Godleski, M.D. - Expert Report from Blaes Case

John Godleski Report - Echeverria

John Godleski Supplemental Report - Echeverria

Hopkins, J. (2015). Letter to Gene M. Williams. Unpublished letter.

Johnson's Baby Powder - website, product description

Kemp Hearing Transcript - Douglas Weed

Longo, Rigler, Egeland. MAS Project 14-1852: Below the Waist Application of Johnson & Johnson Baby Powder, September 2017

Longo, Rigler - Analysis of Johnson & Johnson Baby Powder & Valiant Shower to Shower talc products for amphibole (tremolite) asbestos, August 2017

Longo, Rigler - Analysis Report MAS Project #14-1683 Johnson's Baby Powder Sample Set, April 2017

Longo, Rigler - TEM Analysis of historical 1978 Johnson's Baby Powder Sample for amphibole asbestos, February 2018

Longo, Rigler – Expert Report In re: Talcum Power Prod. Liab. Litig., MDL No. 2738 (November 14, 2018).

"Making it up as he goes along: Paolo Boffetta, Italian Epidemiologist, distorts power line health risks" - https://microwavenews.com/news-center/boffetta-post-truth.

Material Safety Data Sheet from Luzenac America, Inc.; Version 45.0, updated 6/18/08 (Group 1)

Material Safety Data Sheet from Luzenac America, Inc. (Group 3)

Material Safety Data Sheet from Luzenac America, Inc.; Version 2.0, updated 2/26/09 (Group CAN)

Material Safety Data Sheet from Luzenac America, Inc. (Group 1)

MBS Invoices – December 2007, April 2012, May 2013, July 2013, December 20013, January 2015, March 2015

MSDS Sheet, Version 2.0

Muscat, J. E. (2015). Report on the Relationship between Hygienic Use of Talc and the Risk of Ovarian Cancer. Unpublished report.

NPR Article Johnson & Johnson Pledges to Purge Controversial Chemicals April 16, 2015

Ness, R. B. (2015). Report on the question of whether genital talc use causes ovarian cancer. Unpublished report.

Ness, R. Expert Report - Jacqueline Fox

Ness, R. Commentary "A plaintiff's witness in the baby powder case"

NTP "The Report on Carcinogens Tenth Edition - Factsheet"

Omiecinski, C. J. (2015). Opinion on the Relationship Between Chronic Perineal/Genital Exposures to Cosmetic Talc and Ovarian Cancers: Mechanistic Aspects and Biological Plausibility Unpublished report.

Osann, K. (2016). Report on Perineal Talc Exposure and Risk of Ovarian Cancer. Unpublished report.

Personal Care Products Council Letter – July 21, 2009 to FDA re: Comments to FDA Citizen's Petition to the Commissioner of the Food and Drug Administration Seeking a Cancer Warning on Talc Products

Photographs of Johnson's Baby Powder

Photographs of Shower to Shower

Riham Sheble, Shabina Khatri. DOHA News - Johnson's baby powder of Qatar shelvees after US cancer lawsuit verdict

Roe. Controversy: Cosmetic tlac and ovarian cancer (1979)

Rosenthal, G. J. (2015). Opinion on Relationships Between the Toxicology of Cosmetic Talc and the Pathogenesis of Ovarian Cancer. Unpublished report.

Rosenthal, G - Expert Report from Blaes Case: "Opinion on Relationships Between the Toxicology of Cosmetic Talc and the Pathogenesis of Ovarian Cancer"

Rothman, Pastides, Samet. (2000) Interpretation of epidemiologic studies on talc and ovarian cancer

Slemp v. Johnson & Johnson, et al., Trial Transcript

Summary Minutes of the NTP Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee Meeting

Talc Removed from 12th RoC- The Rose Sheet October 24, 2005

WHMIS Classification for Talc, non fibrous - CNESST; CAS Number: 14807-96-6

Weed, Douglas. A Report Regarding General Causation and an Evaluation of the Reliability and Validity of the Plaintiffs' Experts' Reports Designated for the Plaintiff, Lori Oules (Feb. 1, 2017)

17. Curriculum Vitae – Jack Siemiatycki

CURRICULUM VITAE

Jack Siemiatycki

TABLE OF CONTENTS

STATISTICAL SUMMARY OF SELECTED ACCOMPLISHMENTS

Publications in peer-reviewed journals	245
Book chapters, IARC Monographs	20
Other publications, reports	42
Book (authored)	1
Invited presentations	173
Conference presentations, posters, abstracts : offered and accepted	181
Grants received as P.I. (number)	36
Grants received as P.I. ($)	$15.4M
Grants received as co-investigator (number)	59
Grants received as co-investigator ($)	$27.9M
H-factor (google scholar)	64
Instances of participation on expert panels, committees, boards of directors, at invitation of governments or public health agencies or research agencies or universities	126
Grant review panels or referee for external institution or journal editorial boards	65
Honours	several

GENERAL INFORMATION

Work address
Université de Montréal
Research Center of CHUM
850 rue St Denis, Montréal, QC, Canada H2W 1V1

Tel: (514) 890-8166
Fax: (514) 412-7106
E-mail: j.siemiatycki@uMontréal.ca

EDUCATION

1967 B.Sc. (mathematics); McGill University
1970 M.Sc. (mathematical statistics); McGill University
1976 Ph.D. (epidemiology and medical statistics); McGill University
1977 Post-doctoral (cancer epidemiology); International Agency for Research on Cancer, Lyon

CURRENT ACADEMIC APPOINTMENTS

Professor, Department of Social and Preventive Medicine, Université de Montréal (since 2001)
Cancer Research Society-Guzzo Research Chair in Environment and Cancer, Université de Montréal (since November 2007)
Adjunct Professor, Department of Epidemiology, Biostatistics and Occupational Health, McGill University. (since 1979)
Fellow, Canadian Academy of Health Sciences (since 2008)

PREVIOUS ACADEMIC APPOINTMENTS AND WORK EXPERIENCE

1967-71	Research Fellow; Department of Epidemiology and Health, McGill University.
1970-72	Research Director; Pointe St. Charles Community Clinic, Montréal.
1978	Consultant; International Agency for Research on Cancer, Lyon.
1978-2001	Assistant, then Associate (1979), then full Professor (1983): Epidemiology Research Center, Institut Armand-Frappier, Laval, Québec.
1982-1986	Associate member, McGill Cancer Center, McGill University.
1996-1997	Visiting Scientist. International Agency for Research on Cancer, Lyon.
2001-2015	Canada Research Chair (Tier 1), Université de Montréal (resigned 2011).
2003-2009	Affiliate Scientist. McLaughlin Centre for Pop'n Health Risk Assessment, Univ of Ottawa.

SIGNIFICANT INTERNAL ADMINISTRATIVE APPOINTMENTS

1982-86	Director, Équipe associée de l'Institut de Recherche en Santé et Sécurité du Travail sur les cancers professionnels (affiliated research team of the Quebec Institute for Occupational Health and Safety on Occupational Cancer).
1988-91	Director, Epidemiology Research Center, Institut Armand-Frappier.
1990-98	Director, Équipe prioritaire de recherche en épidémiologie environnementale du FRSQ. (Priority research team in environmental epidemiology)
1998-2001	Member, Governing Council (Conseil d'administration). Institut national de la recherche scientifique, Université du Québec.
2000-2007	Coordinator. Program of Research in Environmental Epidemiology of Cancer (PREECAN), a national program funded by the National Cancer Institute of Canada.
2002-2005	Associate Director for Population Health Sciences, Research Center of the University of Montréal Hospital Center.

2006-2007 Director, Epidemiology program, PhD public health, Université de Montréal.
2006-2014 Director, Axe risques à la santé (Health Risks Division). Centre de recherche du Centre hospitalier de l'Université de Montréal.

SIGNIFICANT INSTITUTIONAL COMMITTEES

1979-80 Member of faculty committee to negotiate a collective agreement with the Institut Armand-Frappier administration.
1982-92 Member, Research Council. Institut Armand-Frappier.
1998-2001 Member, Institutional advisory council. Institut Armand-Frappier. Institut national de la recherche scientifique
2002-2006 Comité de direction. Centre de recherche du CHUM
2002-2017 Member, Various committees of the Dept Med Soc et Preventive, including Promotions, and Recruitment.
2006-2009 Member, Various committees established to set up a new School of Public Health at l'Université de Montréal
2006-2014 Comité Scientifique de la Recherche du CHUM.

CURRENT MAJOR EXTERNAL BOARDS, SCIENTIFIC COMMITTEES (INVITED)

1. Chair of Scientific Advisory Committee of CONSTANCES, a large prospective cohort established in France, under aegis of INSERM, Ministère de la Santé, and other agencies. Since 2011.
2. Member of Comité national d'épidémiologie en cancérologie. Ministère de la Santé et des Services sociaux, Quebec. Since 2014.
3. Member, Advisory committee to Directors of Cartagene, a Quebec population cohort.

PAST MAJOR EXTERNAL BOARDS, SCIENTIFIC COMMITTEES, CONSULTATIONS (INVITED)

1. Expert consultative committee to Commission de la santé et sécurité du travail du Québec on the epidemiologic function of the CSST. 1979-80.
2. President of Organizing Committee of Annual Congress of Quebec Public Health Association, Montréal. 1982.
3. Consultative committee of International Agency for Research on Cancer on feasibility of SEARCH programme. 1982.
4. Canadian representative. International Joint Commission (U.S. and Canada) Committee on the Assessment of Human Health Effects of Great Lakes Water Quality. 1982-89.
5. Task Force on Chemicals in the Environment and Human Reproduction Effects in New Brunswick. 1983-85.
6. Chairman and organizer of international workshop sponsored by International Agency for Research on Cancer, Lyon, on use of job exposure information in cancer case-control studies. 1984.
7. Quebec Government Consultative Committee on Alachlor. 1985-86.
8. Chairman and organizer of the International Joint Commission Workshop on the Role of Epidemiology in Assessing the Effects of Great Lakes Water Quality on Human Health, Scarborough, March 1988. 1986-88.
9. Priority Substances Advisory Panel. Panel established under terms of Canadian Environmental Protection Act by Health and Welfare Canada. 1988.
10. Working Group on Electromagnetic Fields under auspices of Health Effects Institute. 1991.
11. Consultative Committee on Environment-related Cancer Surveillance, LCDC, Health and Welfare Canada. 1993-1996.
12. Consultative Committee on an Investigation of Lung Cancer and Environmental Tobacco Smoke, Environmental Health Directorate, Health Canada. 1994-1995.
13. Working Group on Evaluation of Carcinogenicity of Carbon Black, Printing Trades and Various Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, 1995.

14. Working Group on Human Cancer Risks associated with Chrysotile Asbestos. World Health Organization (IPCS) Geneva, June 1995.
15. Secretariat on Evaluation of Chemopreventive Effect of Aspirin and Other NSAIDS for Cancer. International Agency for Res. on Cancer, Lyon, Apr. 1997.
16. Chair. Symposium on Health Risks of Water Disinfection By-products. Convened by Health Canada. Ottawa. May 1997.
17. Working Group. Meeting on Species-specificity in response to carcinogens. Monograph Programme. International Agency for Res. on Cancer, Lyon, Nov. 1997.
18. Board of Directors. Canadian Society for Epidemiology and Biostatistics. 1997-1999.
19. Working Group. Evaluation of Carcinogenicity of Various Industrial Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, Feb. 1998.
20. Canadian Coalition on Cancer Surveillance. 1997-2002.
21. External site review panel. U.S. National Cancer Institute Epidemiology Branch. June 1999.
22. Organizing Committee for Medical Research Council Workshop on Privacy of Health Data. 1999-2000.
23. Organizing Committee, EPI2001. Joint North American Congress of Canadian Society for Epidemiology and Biostatistics, Society for Epidemiologic Research, American Public Health Association (Epid) and American College of Epidemiology, Toronto, 14 – 16 June 2001. 1999-2001.
24. Coordinator of national initiative of the public health community to provide guidance on the structures and functioning of the new Canadian Institutes of Health Research. 1999-2000.
25. Organizing Committee. World Congress of the International Epidemiological Association, Montréal, 18-22 August 2002. 2001-2002.
26. President. Canadian Society for Epidemiology and Biostatistics. 2001-2003. Member of Board. 1997-1999.
27. Working Group. Evaluation of Carcinogenicity of Various Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, 2003.
28. Jury of Consensus Conference on risks and benefits of vaccination for hepatitis B. For Minister of Health of France. Organized by INSERM and ANAES. Paris 2003.
29. Public Advisory Panel. Vinyl Council of Canada. 1998-2004.
30. Advisory Panel. U.S. National Cancer Institute Brain Tumor Study. 1998-2003.
31. Scientific Advisory Committee. Boeing/UAW Workers' Health Studies. 1999-2005.
32. Institute Advisory Board. Canadian Institutes for Health Research – Institute of Circulatory and Respiratory Health. 2001-2005.
33. National Occupational Research Agenda (NORA). Joint consultative committee for US National Cancer Institute and US National Institute for Occupational Safety and Health. 2002-2005.
34. Canadian Cancer Surveillance Alliance. Consultative committee of Health Canada, Canadian Cancer Society, Provincial Cancer Registries, Statistics Canada. 2002-2003.
35. Co-president. Organizing Committee of Joint SER-CSEB Congress, Toronto 27-30 June 2005. (2004-2005).
36. Chair. Monograph Program Meeting. International Agency for Research on Cancer (WHO), France. February 2006.
37. Advisory Committee on Research Ethics and Databanks. Quebec Health Research Council (FRSQ). 2003-2011.
38. Board of Directors. American College of Epidemiology. 2003-2006.
39. Board of Directors. National Cancer Institute of Canada. 2003-2007.
40. Member Scientific Council International Agency for Research on Cancer (WHO). Lyon, France 2005-2009.
41. Elected Chair. Scientific Council International Agency for Research on Cancer (WHO). Lyon, France 2008-2009.
42. Scientific Advisory Council Canadian Partnership Against Cancer 2007-2009.
43. Advisory Committee. Occupational Cancer Research Centre of Ontario. Since 2009.
44. Working Group on Cancer Prevention, CPAC, 2007-2010.

45. Subgroup Chair and Working Group Member. Evaluation of Carcinogenicity of Non-Ionizing Radiation, Radiofrequency Electromagnetic Fields. Monograph Programme. International Agency for Research on Cancer, Lyon May 2011.
46. Member of Scientific Advisory Board of Bordeaux cancer research center SIRIC-BRIO, Bordeaux France. Since 2013.
47. Member of external review panel. Helmholtz Center Munich Research Institute. Germany. July 2011.
48. Conseil Scientifique de l'Institut de Recherche en Santé Publique (IReSP). Under aegis of INSERM and Ministère de la Santé, France. 2004-2009.
49. Adviser and expert witness for legal team conducting a major class action lawsuit against the Canadian tobacco industry. 2007-2014.

OTHER SIGNIFICANT EXTERNAL CONSULTATIONS (INVITED)

1. Consultation with Quebec Ministry of Justice regarding compensation for homeowners who were advised to use formaldehyde-base home insulation - 1983.
2. Invited participant. Workshop convened by the Science Council of Canada on the future of Epidemiology in Canada, Ottawa - 1985.
3. Consultation with Government of Alberta regarding the evaluation of a report alleging significant health impact in the environment of a sour-gas plant - 1985.
4. Consultation with Quebec Ministry of Environment regarding health effects of residency near an abandoned toxic waste site in LaSalle, Quebec - 1987.
5. Invited participant. Workshop convened by Canadian Public Health Association, Environment Canada and Health and Welfare Canada on Environmental Impact Assessment, Ottawa - 1987.
6. Invited participant. Annual workshops convened by Health Protection Branch of Health and Welfare Canada to discuss the role of Canada in the SEARCH programme of the International Agency for Research on Cancer, Ottawa - 1987-1989.
7. Consultation with Quebec Cree Band Council regarding a research proposal to study developmental effects of consuming fish with high mercury levels - 1989.
8. Invited participant. Workshop convened by Ontario Industrial Disease Standards Panel on the use of epidemiologic data in workers' compensation, Toronto - December 1989.
9. Invited participant. Workshop convened by National Academy of Sciences (U.S.) on Carcinogenicity of Complex Mixtures, Tucson, Arizona - Jan 1990.
10. Invited participant. Workshop convened by Laboratory Centers for Disease Control, Health and Welfare Canada on Multiple Chemical Sensitivities, Ottawa - May 1990
11. Member of expert advisory panel to the pan-Canadian case-control study of electromagnetic fields and childhood leukemia. Sponsored by Canadian Electrical Assoc, EPRI (U.S.A.), Health and Welfare Canada. 1990-1996.
12. Organizer of Workshop to Plan a Pan-North American Case-control Study of Lung Cancer. Sponsored by Health and Welfare Canada. Toronto. March 1991.
13. Invited participant. Workshop convened by Environmental Health Directorate of Health and Welfare Canada, on Environmental Epidemiology in Canada. Ottawa. March 1992
14. Invited participant. Workshop convened by Harvard Center for Risk Analysis on implementing a new type of risk assessment. Maryland. April 1992.
15. Member of Technical Advisory Panel for epidemiology studies of foundry workers - CIIT. Research Triangle Park, N.C. Feb. 1993
16. Consultant to Health Effects Institute - Asbestos Research, on Options for Characterizing Worker Activities in Buildings, Boston. Feb. 1993.
17. Advisory panel to Laboratory Centers for Disease Control, Health and Welfare Canada, on Environmental Epidemiology under the Green Plan. March 1993.
18. Member of External Advisory Committee. Champlain Adirondack Biosphere Environmental Health Sciences Center, University of Vermont. 1993.
19. Consultant to Michigan Cancer Foundation on a variety of epidemiologic studies. 1993-1996.

20. Invited to address President Clinton's Panel on Cancer regarding priorities in cancer research. Bethesda, MD. April 1994.
21. Invited participant. Science and Technology Review Consultation. Government of Canada. Montréal. September 1994.
22. Invited participant. Strategic planning workshop to reduce Environmental Tobacco Smoking exposure. Laboratory Centre for Disease Control. Health Canada. Oct 1995.
23. Invited participant. Meeting to establish new priorities for funding. National Health Research and Development Programme of Canada. Montréal. Feb 1996.
24. Chair Scientific Advisory Committee for the Dalhousie University study of health effects of environmental and occupational pollution in the area of the Sydney, Nova Scotia steel industry. 1996.
25. Member of two Ministerial missions of the Quebec and Canadian governments to France to discuss with French experts the risks associated with low level exposure to chrysotile asbestos. Paris. Oct 1996.
26. Chair. Meeting of collaborators of European network of studies on lung cancer and smoking.
27. International Agency for Res. on Cancer, Lyon. June 1997.
28. Member of Canadian scientific delegation to United Kingdom to discuss with British experts the risk associated with low level exposure to chrysotile asbestos. London, Sept. 1997.
29. Symposium chair. Workshop to discuss methods of predicting numbers of cases of mesothelioma to be expected in various countries. Paris. Dec. 1997.
30. Invited participant and subgroup reporter. Peer Review on Hazard Assessment and Dose-Response Characterization for the Carcinogenicity of Formaldehyde by the Route of Inhalation. Health Canada and U.S. EPA. Ottawa. March 1998.
31. Co-chair. Workshop to explore the feasibility of an international collaborative study on use of cellular phones and risk of cancer. International Agency for Research on Cancer. Lyon. Feb 1999.
32. Panellist. Consensus Meeting for a Proposed Integrated National Health Surveillance Network. Health Canada. 1999.
33. Invited participant. Medical Research Council Summit Meeting on the new Canadian Institutes of Health Research. Toronto. June, 1999.
34. Invited participant. Planning group for an Institute of Population Health Research in CIHR. Jul-Dec 1999.
35. Invited speaker. Workshop for a Canadian Institute for Genetics Research. May 2000.
36. Invited participant. Workshop to explore the use of prospective cohorts to investigate gene-environment interactions in cancer etiology. National Cancer Institute. Rockville, MD. May 2000.
37. Invited participant. Founding meeting of Canadian Association for Workplace Safety and Health. Montréal. Jan 2001.
38. Invited participant. Workshop to advise Canadian Foundation for Innovation on its role in supporting population health research in Canada. Toronto, Feb 2001.
39. Invited participant. Consultative committee to advise Cancer Care Ontario on priorities in environmental cancer. April 2001.
40. Invited participant. Workshop on national priorities in cancer research. Institute for Cancer Research. CIHR. Toronto. May 2001.
41. Invited participant. Delphi process to advise Canadian Institutes of Health Research on priorities in cancer research. October-December 2001.
42. Invited participant. Delphi process to advise Cancer Care Ontario on priorities in cancer prevention. November-April 2002.
43. Session Chair. NIOSH workshop "Applying New Biotechnologies to the Study of Occupational Cancer", Washington, D.C. May 2002.
44. Member of Advisory Panel. U.S. National Cancer Inst. Study of a Cohort of Chinese Workers Exposed to Benzene. 2002- .
45. Invited participant. Delphi process to advise Cancer Care Ontario on priorities in cancer prevention. November-April 2002.
46. Session Chair. NIOSH workshop "Applying New Biotechnologies to the Study of Occupational Cancer", Washington, D.C. May 2002.

47. Organizer and Session Chair. International Epidemiological Association Meeting. Occupation and Health. Montréal. August, 2002.
48. Co-Organizer and Session Chair. Epidemiological Association Meeting. Asbestos and mesothelioma. Montréal. August, 2002.
49. Session Chair. Epidemiological Association Meeting. Environment and Health. Montréal Aug, 2002.
50. Invited participant. CIHR National Forum to devise a National Research Programme for Environmental Health. Ottawa. Sept 2002.
51. Invited participant. CIHR national forum on privacy of health data. Ottawa, November, 2002.
52. Member. Environmental and Occupational Carcinogens Advisory Group. Canadian Cancer Society. 2002 - 2004.
53. Participant. Meeting to discuss the establishment of a prospective childhood cohort in Canada. CIHR-IPPH. March 2004.
54. Member of working group on national cohort project. National Cancer Research Initiative. January-June 2004.
55. Member of advisory group on development of IDEES, Université de Montréal. January-June 2004.
56. Member, ad-hoc group to explore the feasibility of a Canadian cohort on cancer and chronic disease. 2004-2008.
57. Invited participant. Workshop to discuss the enhancement of population health research in Canada. CIHR-IPPH. June 2004.
58. Invited participant. Workshop on occupational cancer surveillance. Occupational Cancer Research & Surveillance Project (Cancer Care Ontario and the Ontario Workplace Safety & Insurance Board). February 2005.
59. Invited participant. Workshop on long-term large-scale cohorts. CIHR, December 2005.
60. Member. Advisory Scientific Committee. IBM – University of Alabama project on health of IBM manufacturing plant workers. 2006 - 2008.
61. Advisor and meeting participant. Ontario Workplace Safety and Insurance Board. Recommendations on how to develop occupational cancer research in Ontario. Toronto, 2005.
62. Invited participant. Workshop to estimate the burden of occupational cancer in the United Kingdom. UK Health and Safety Executive. Manchester. June 2006.
63. Advisory Committee to British Energy Networks Association. Workshop on the Future Needs of Electro-magnetic Fields Occupational Studies in the Electric Utility Industry. Edinburgh. September 2006.
64. Advisory Committee. IARC Monograph Programme Planning of Special Volume 100. Lyon. September 2006.
65. Grant Review Panel. IVRSP. Paris. September 2006.
66. Advisory Committee to CCRA and ICR (CIHR) on the nature of a national cohort platform. Toronto, September 2006.
67. Invited participant. Comité d'éthique de la recherche de la faculté de médecine (CERFM) : Discussion d'un projet soumis pour la création d'une banque de données et de matériaux biologiques (Research Ethics Committee of the Faculty of Medicine: Review of a submitted project to create a bank of data and biologic samples). Université de Montréal. March 2007.
68. Invited participant. Workshop to Design and Implement the Ontario Cohort Consortium Research Platform. Toronto. June 2007.
69. Invited participant. Canadian Cancer Research Agencies. Strategic Planning Consultation in Montréal. May 2009.
70. Invited participant. IARC-NORA workshop to identify gaps of knowledge on occupational carcinogens, Lyon. June 2009.
71. Consultant. State of the science workshop: evaluation of epidemiological data consistency for application in regulatory risk assessment. US EPA and Johns Hopkins School of Public Health. Baltimore. September 2010.
72. Consultant. World Health Organisation. Re-evaluation of Risk Assessments related to DDT exposure. Geneva. November 2010.

73. Invited participant. WHO workshop to develop international guidelines for control of environmental carcinogens. Asturias. March 2011.
74. Session Chair. Discovering occupational carcinogens. Congress of Epidemiology. Montréal June 2011.
75. Invited co-organiser. Symposium of Environment and Cancer. Canadian Cancer Research Conference. Toronto. November 2011.
76. Invited organiser and Chair. Symposium on Cellphones and Cancer. American Association for Cancer Research. Chicago, April 2012.
77. Member Scientific Program Committee for the 2013 Canadian Cancer Research Conference, Toronto. November 2013.
78. Member of Advisory Committee to National Cancer Institute (U.S.) study on carcinogenicity of diesel emissions. 2017.

HONOURS

1. Biographee in various Who's Who in America versions. Since 1982
2. Perron-Desrosiers Prize. Granted by the Governing Council of the Institut Armand-Frappier. 1985.
3. Invited to give the annual Elizabeth Stern Memorial Lecture in U.C.L.A. School of Public Health. 1985.
4. National Health Scholar. National Health Research and Development Programme of Canada. 1988-1998.
5. Visiting Scientist Award. International Agency for Research on Cancer, Lyon. 1996-97.
6. Prix d'excellence. Institut national de la recherche scientifique. Université du Québec. 1999.
7. Distinguished Scientist Award. Medical Research Council, Canada. 1999-2004.
8. Canada Research Chair in Environmental Epidemiology and Population Health. 2001-2015.
9. Distinguished Scientist Lecturer. US National Cancer Institute. Division of Cancer Epidemiology and Genetics. 2006.
10. Cancer Research Society–Guzzo Chair in Environment and Cancer. Since 2007.
11. Fellow Canadian Academy of Health Sciences. Since 2008.
12. Geoffrey R Howe Distinguished Contributions Award, Canadian Society for Epidemiology & Biostatistics. 2011.
13. Ranked top Canadian public health researcher in terms of research productivity by Jarvey et al. 2012.

GRANT REVIEW, JOURNAL REVIEW AND PERSONNEL REVIEW

Associate Editor

American Journal of Epidemiology (1989-1998)
International Journal of Environmental Health (1991-)

Contributing Editor

Journal of Public Health Policy (1982-87)
American Journal of Industrial Medicine (1996-)
The Open Epidemiology Journal (2007-)

Chairman of grant review panels

National Health Research and Development Programme. Canada. (1990-94)
National Cancer Institute of Canada (1994-1995)

Member of grant review panels

40 times

External referee for tenure or promotion of personnel in other institutions

15 times

THESES

1. Siemiatycki J. "Space-time clustering: finding the distribution of a correlation-type statistic". M.Sc. thesis, McGill University, 1971.
2. Siemiatycki J. "Evaluation of strategies for household health surveys". Ph.D. thesis, McGill University, 1976.

ARTICLES PUBLISHED PEER REVIEW

1. Thurlbeck WM, Horowitz I, Siemiatycki J, Dunnill MS, Maisel JC, Pratt P, et al. Intra- and inter-observer variations in the assessment of emphysema. Archives of Environmental Health. 1969;18:646-59.
2. Becklake MR, Fournier-Massey G, McDonald JC, Siemiatycki J, Rossiter CE. Lung function in relation to chest radiographic changes in Quebec asbestos workers. Bulletin de Physio-Pathologie Respiratoire. 1970;6:637-59.
3. McDonald JC, McDonald AD, Gibbs GW, Siemiatycki J, Rossiter CE. Mortality in the chrysotile asbestos mines and mills of Quebec. Archives of Environmental Health. 1971;22:677-86.
4. Siemiatycki J, McDonald AD. Neural tube defects in Quebec: a search for evidence of `clustering' in time and place. British Journal of Preventive and Social Medicine. 1972;26:10-4.
5. Siemiatycki J. Mantel's space-time clustering statistic: computing higher moments and a comparison of various data transforms. Journal of Statistical Computation & Simulation. 1978;7:13-31.
6. Siemiatycki J. A comparison of mail, telephone, and home interview strategies for household health surveys. American Journal of Public Health. 1979;69(3):238-45.
7. Siemiatycki J, Brubaker G, Geser A. Space-time clustering of Burkitt's lymphoma in east Africa: analysis of recent data and a new look at old data. International Journal of Cancer. 1980;25:197-203.
8. Siemiatycki J, Richardson L. Statut socio-économique et utilisation des services de santé à Montréal. L'Actualité Economique. 1980(Avril-Juin):194-210.
9. Siemiatycki J, Richardson L, Pless IB. Equality in medical care under national health insurance in Montréal. New England Journal of Medicine. 1980;303:10-5.
10. Colle E, Siemiatycki J, West R, Belmonte MM, Crepeau MP, Poirier R, et al. Incidence of juvenile onset diabetes in Montréal - demonstration of ethnic differences and socio-economic class differences. Journal of Chronic Diseases. 1981;34(12):611-6.
11. Siemiatycki J, Day NE, Fabry J, Cooper JA. Discovering carcinogens in the occupational environment: a novel epidemiologic approach. Journal of the National Cancer Institute. 1981;66(2):217-25.
12. Siemiatycki J, Thomas DC. Biological models and statistical interactions: an example from multistage carcinogenesis. International Journal of Epidemiology. 1981;10(4):383-7.
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BOOK CHAPTERS (invited) AND IARC MONOGRAPHS

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94. Siemiatycki J. An empirical evaluation of the magnitude of confounding bias. Statistical Society of Canada, Waterloo, June 1996.

95. Siemiatycki J. Occupational exposures and cancer risk: recent results and methodological insights from a population-based case-control study in Montréal. Department of Epidemiology & Biostatistics, McGill University. October, 1996.
96. Siemiatycki J. Utilités et limites des études épidémiologiques dans l'évaluation des risques environnementaux. ACFAS, City of Québec, Quebec, May 1998.
97. Siemiatycki J. International collaboration in cancer epidemiology. Society for Epidemiology Research, Chicago, June 1998.
98. Siemiatycki J. Accuracy of the EPA risk assessment model for predicting the risk of lung cancer at environmental levels of asbestos exposure. National Cancer Institute, Rockville, Maryland, March 1999.
99. Siemiatycki J. Risk of lung cancer at environmental levels of asbestos exposure. University of Toronto, Toronto, September 1999.
100. Siemiatycki J. Estimating risks due to low level exposures. Society for Epidemiology Research, Seattle, June 2000.
101. Siemiatycki J. Debater on the proposition that research is a top priority in occupational cancer prevention. Preventive Oncology Seminar, Cancer Care Ontario, Toronto, April 2001.
102. Rachet B, Siemiatycki J, Abrahamowicz M, Leffondre K. Various aspects of smoking behavior on lung cancer risk: a flexible modeling approach. National Cancer Institute, Bethesda, May 2001.
103. Siemiatycki J. Challenges to epidemiology and challenges to Canadian epidemiologists. National Student Conference of Epidemiology, Toronto, June, 2001.
104. Siemiatycki J. President's address. Congress of Epidemiology, Toronto, June, 2001.
105. Siemiatycki J. Découvrir les cancérigènes dans l'environnement: bilan des activités de recherche passées et perspectives d'avenir. Département de médecine sociale et préventive, Université de Montréal, October 2001.
106. Siemiatycki J. Risque de cancer chez les femmes résidantes des villes des mines d'amiante québécoises: Évaluation du risque attribuable à des « faibles » niveaux d'expositions et validation de la méthode d'évaluation de risque (« risk assessment ») du E.P.A. Département de santé environnementale, Université de Montréal, October 2001.
107. Rachet B, Siemiatycki J, Leffondre K, Abrahamowicz M. Relations dose-réponse entre la fumée de cigarette et le cancer pulmonaire à partir d'une étude cas-témoins à Montréal : Estimations utilisant une modélisation flexible. Congrès INRS-Institut Armand-Frappier, Sainte-Adèle, Quebec, November 2001.
108. Siemiatycki J, Camus M, Case B, Desy M, Parent, M.-É. Risque de cancer chez les résidantes des villes de l'amiante au Québec: Évaluation du risque attribuable à des « faibles » niveaux d'expositions et validation de la méthode d'évaluation de risque de l'E.P.A. Symposium sur l'amiante of Institut national de santé publique du Québec, Montréal, December 2001.
109. Laplante O, Parent M.-É, Siemiatycki J. Risque de mésothéliome et de cancer du poumon associé à l'exposition professionnelle aux fibres d'amiante, Montréal 1979-85. Symposium de l'Institut national de santé publique du Québec, Montréal, December 2001.
110. Siemiatycki J. Occupational causes of cancer: overview of the contribution of a study in Montréal, Research Day at Dept of Epidemiology and Community Medicine, University of Ottawa, April 2002.
111. Siemiatycki J. Biostatistical problems in epidemiologic case-control studies. Statistical Society of Canada, Hamilton, Ontario, May 2002.
112. Leffondre K, Abrahamowicz M, Siemiatycki J. Definition of risk sets for Cox's analysis of case-control data with time-varying exposures: A simulation study. Intended Society for Clinical Biostatistics (ISCB), Dijon, France, September 2002.
113. Siemiatycki J. Occupational causes of cancer. CCERN and Health Canada Research Workshop, Montebello, Quebec. October 2002.
114. Siemiatycki J. Occupational causes of cancer. Departmental seminar, McGill University, Montréal. November 2002.
115. Siemiatycki J. Facteurs environnementaux dans l'étiologie du cancer. Retraite annuelle du centre de recherche du CHUM, St-Sauveur, Quebec. November 2002.
116. Siemiatycki J. Environmental and occupational causes of cancer. Seminar. Cancer Care Ontario, Toronto, February 2003.

117. Siemiatycki J. The state of epidemiology in Canada. Plenary address. CSEB Student Congress, Halifax, Nova Scotia, June 2003.
118. Siemiatycki J. Occupational cancer epidemiology: the evolving big picture. Distinguished Scientist Lecture, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville MD, October 2003.
119. Siemiatycki J. Challenges in cancer epidemiology. Meeting of the Institute Advisory Board of Institute for Cancer Research, CIHR, Montréal, June 2004.
120. Siemiatycki J. Keynote address. Occupation and cancer. International Association of Cancer Registries, Beijing, September 2004.
121. Siemiatycki J. Which cancers are most important, what are the associated occupational situations and which confounders are involved? Burden of Cancer Epidemiologic Workshops, Health and Safety Executive. Manchester, UK, November 2004.
122. Siemiatycki J. Occupational causes of cancer. New Strategies for Recognizing and Preventing Occupational Disease, Canadian Center for Occupational Health and Safety, Toronto, March 2005.
123. Siemiatycki J. Occupational causes of cancer. The Respiratory Epidemiology & Clinical Research Unit, Montréal Chest Institute, Montréal, March 2005.
124. Siemiatycki J. Environnement et cancer : quels sont les risques? Les Belles Soirées public lecture series, Université de Montréal, Montréal, April 2005.
125. Siemiatycki J. An overview of environmental, occupational & lifestyle causes of lung cancer. Cancer Axis, McGill University Hospital Centre Research Institute, Montréal, June 2005.
126. Siemiatycki J. Les règles des comités d'éthique vont amputer notre capacité de prévenir des maladies et sauver des vies. Réunion de FRSQ sur les banques de données et des matières biologiques, Montréal, June 2005.
127. Siemiatycki J. Introductory comments. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
128. Siemiatycki J. The burden of occupational cancer on workers and on society. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
129. Siemiatycki J. Revue des expositions professionnelles associées au cancer (Review of occupational exposures associated with cancer): pre-conference training session. Environnement et santé. Congrès international de l'Association des Épidémiologistes de Langue Française (ADELF), City of Québec, Quebec, September 2005.
130. Siemiatycki J. Opening session. Environnement et santé. Congrès international de l'Association des Épidémiologistes de Langue Française (ADELF), City of Québec, Quebec, September 2005.
131. Siemiatycki J. Impact de l'environnement et du milieu de travail sur le cancer : connaissances récentes. 9es Journées annuelles de santé publique (JASP), City of Québec, Quebec, November 2005.
132. Siemiatycki J. La recherche épidémiologique sur le cancer. Canadian Cancer Society - 2005 Annual Conference, City of Québec, Quebec, November 2005.
133. Siemiatycki J. Occupational EMF exposure and risk of cancer – methodological considerations. Workshop on the Future Needs of Electro-magnetic Fields Occupational Studies in the Electric Utility Industry, Edinburgh, September 2006.
134. Siemiatycki J. What is known about the modifiable causes of cancer and why we will not learn much more: Reflections on the decline of epidemiology as a tool to elucidate disease etiology. Department of Epidemiology, Biostatistics & Occupational Health, McGill University, Montréal, October 2006.
135. Siemiatycki J. Keynote Speaker. Environmental causes of cancer. 28th Annual Meeting of the International Association of Cancer Registries, Goiania, Brazil, November 2006.
136. Parent M.-E, Rousseau M.-C, Siemiatycki J, Boffetta P, Cohen A. Using the workplace as a window to study the role of diesen and gasoline engine emissions in lung cancer developpement. Invited abstract submitted to the Eleventh International Congress of Toxicology, Montréal, Quebec, July 2007.
137. Siemiatycki J. Keynote Speaker. The future of occupational epidemiology? 19th International Conference on Epidemiology in Occupational Health (EPICOH 2007), Banff, October 2007. Occup. Environ. Med. 2007 Dec; 64:46.

138. Siemiatycki J. Relationship between environmental risks and health of seniors. Workshop on Seniors' Health and the environment. Health Canada, Ottawa, February 2008.
139. Siemiatycki J. Freedom of research - is it threatening or threatened? Conference of Institutional Review Boards of Quebec, (4e Journées d'étude des CER), City of Québec, Quebec, October 2008.
140. Siemiatycki J. Cancer and Environment – Annual University of Montréal Medical Faculty Assembly, Montréal, December 2008.
141. Siemiatycki J. Impact de l'environnement et du milieu de travail sur les risques de cancer : méthodologie de recherche et résultats. Conférence en santé publique, Université Laval, May 2009.
142. Siemiatycki J. CIHR and Epidemiologic Research. CSEB, Ottawa, May 2009.
143. Siemiatycki J. Mode de vie, milieu de vie: les causes modifiables du cancer. (Lifestyles and environment: modifiable causes of cancer). Keynote address. Conference nationale pour vaincre le cancer, Montréal April 2010.
144. Siemiatycki J. Montréal case-control studies on occupation and cancer. Presentation for II International Course on occupational cancer. Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
145. Siemiatycki J. Modifiable causes of cancer and estimates of attributable fractions. Presentation for II International Course on occupational cancer, Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
146. Siemiatycki J. Asbestos and cancer in Quebec: a presentation of studies in three populations. Presentation for II International Course on occupational cancer. Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
147. Siemiatycki J. An overview of recognized environmental and lifestyle causes of cancer, and their contribution to the overall burden of cancer. International Congress of Pathophysiology, Montréal, September 2010.
148. Siemiatycki J. Les causes modifiables du cancer (Lifestyles and environment: modifiable causes of cancer). Conference annuelle de la Société du cancer du Canada, division Québec, November 2010.
149. Siemiatiycki J. Alison McDonald's research on the impact of Medicare in Québec. Department of Epidemiology and Biostatistics, McGill University, Montréal, Quebec, May 2011.
150. Siemiatycki J. An overview of environmental causes of cancer. Special Symposium to honour Nobel Prize winner CRCHUM, Montréal, Quebec, June 2011.
151. Siemiatycki J. Review of IARC evaluation on cellphones and cancer. Congress of Epidemiology, Montréal, Quebec, June 2011.
152. Siemiatycki J. L'évidence concernant les risques de cancer liés à l'utilisation du téléphone cellulaire. Institut national de santé publique du Québec, October 2011.
153. Siemiatycki J. Do cellphones cause brain cancer? Canadian Cancer Research Conference, Toronto, November 2011.
154. Siemiatycki J. Do cellphones cause brain cancer? Canadian Center for Architecture. Public science lecture series, Montréal, Quebec, January 2012.
155. Siemiatycki J. Do cellphones cause brain cancer? McGill University Department of Epidemiology lecture series, Montréal, Quebec, March 2012.
156. Siemiatycki J. L'environnement et le risque de cancer. Table ronde. Conference annuelle de la Coalition Cancer, Montréal, Quebec, March 2012.
157. Siemiatycki J. An Overview of Modifiable Risk Factors for Cancer. CHUM Department of Medicine, Montréal, Quebec, March 2012.
158. Siemiatycki J. Do cell phones cause brain cancer? The epidemiologic evidence. Grand Rounds, St-Mary's Hospital, Montréal, Quebec, September 2012.
159. Siemiatycki J. The epidemiology of cell phones and brain cancer. Centre hospitalier universitaire Vaudois, Lausanne, Suisse, October 2012
160. Siemiatycki J. Occupational causes of cancer. Annual meeting of Occupational & Environmental Medical Association of Canada, Montréal, Quebec, September 2013.
161. Siemiatycki J. Fraction of lung cancer that is legally attributable to smoking: a novel parameter. ISPED, Bordeaux, France, November 2013.

162. Siemiatycki J. Some challenges in environmental cancer research. Boston University School of Public Health, Boston, Massachusetts, February 2014.
163. Siemiatycki J. Les causes modifiables du cancer: le cancer peut être évité. Symposium de La Fondation Sauve Ta Peau, Montréal, Quebec, September 2014.
164. Siemiatycki J. Using epidemiologic research to combat the tobacco industry. BIPS, Bremen, Germany, September 2015.
165. Siemiatycki J. Insights into the use of epidemiologic data in a class action lawsuit against the tobacco industry. CRCHUM division seminar, Montréal, Quebec, September 2015.
166. Siemiatycki J. Development of a methodology to estimate legally attributable fraction of lung cancer attributable to cigarette smoking. McGill Univ Dept of Epidemiology, Montréal, Quebec, October 2015.
167. Siemiatycki J. Using epidemiologic research to combat the tobacco industry. SIRIC-BRIO Cancer Centre. Bordeaux, France, November 2015.
168. Siemiatycki J. Do cell phones cause brain cancer? The epidemiologic evidence. Dept of Medicine, CHUM, Montréal, Québec, November 2015.
169. Siemiatycki J. Occupation and cancer. Conference for the 50th Anniversary of IARC, Lyon, June 2016.
170. Siemiatycki J. Contribution of epidemiology to knowledge on occupational risk factors for cancer. 34e Congrès national de Médecine et Santé au Travail, Paris, France, June 2016.
171. Siemiatycki J. The influence of JC McDonald on the evolution of epidemiology in Canada. Symposium in honour of JC McDonald. McGill Univ., Montréal, Quebec, May 2017.
172. Siemiatycki J. A survey of knowledge on occupational causes of cancer. Keynote address. International Association of Cancer Registries, Utrecht, Netherlands, October 2017.
173. Siemiatycki J. La preuve statistique au tribunal : recours collectif en situation d'incertitude. Café-statistique de la Société des statisticiens français de la région parisienne, Paris, France, May 2018.

SCIENTIFIC PRESENTATIONS - OFFERED AND ACCEPTED

1. Siemiatycki J. Comparison of mail, telephone and home interview methods for health surveys. International Epidemiologic Association Meeting. Puerto Rico. August 1977.
2. Siemiatycki J, Day NE, Fabry J, Cooper, JA. Identification d’agents cancérigènes dans le milieu de travail: un nouveau système épidémiologique de monitoring. Deuxième conférence internationale sur la science des systèmes dans le domaine de la santé. Montréal, July 1980.
3. Siemiatycki J, Richardson L, Pless B. Equality in Medical Care under National Health Insurance in Montréal. Deuxième conférence internationale sur la science des systèmes dans le domaine de la santé. Montréal, July 1980.
4. Siemiatycki J. Discovering occupational carcinogens. International Symposium on Chemical Mutagenisis, Human Population Monitoring and Genetic Risk Assessment. Ottawa. October 1980.
5. Siemiatycki J, Richardson L, Gerin M. Discovering occupational carcinogens by a substance-based case-control approach-fieldwork considerations. International Epidemiologic Association Meeting. Edinburgh. August 1981.
6. Siemiatycki J, Colle E, West R, Belmonte M. Space-time clustering of juvenile-onset diabetes in Montréal. International Epidemiologic Association Meeting. Edinburgh. August 1981.
7. Siemiatycki J, Gerin M, Richardson L. Discovering occupational carcinogens by an exposure-based case-control approach: exposure assessment aspects. Second International Symposium on Epidemiology in Occupational Health. Montréal, August 1982.
8. Siemiatycki J, Gerin M, Lakhani R, Dewar R, Pellerin J, Richardson L. Nickel and ancer associations from a multicancer occupation exposure case-referent study. Symposium on Nickel in the Environment. Lyon, March 1983.
9. Gerin M, Siemiatycki J. La traduction des histoires professionnelles en histoires d’expositions chimiques: un défi pour l’hygiéniste du travail. Congrès de l’Association pour l’hygiène industrielle du Québec. Quebec, May 1983.
10. Siemiatycki J, Colle E, Campbell S, Belmonte M. Preliminary analysis of a case-control study of Type I diabetes mellitus. Baltimore, June 1985.

11. Siemiatycki J, Richardson L, Gerin M, Goldberg M, Dewar R. Associations between nine sites of cancer and nine organic dusts: results from a hypothesis-generating case-control study in Montréal. Society for Epidemiologic Research. Chapel Hill, North Carolina, June 1985.
12. Richardson L, Siemiatycki J, Gerin M, Goldberg, M, Dewar R, Desy M, Campbell S, Wacholder S. Associations between several sites of cancer and nine organic dusts: results from a case-control study. Fourth International Symposium on Epidemiology in Occupational Health. Como, Italy, September 1985.
13. Richardson L, Siemiatycki J. Case-control study methods: when to interview subjects and non-response bias. Fourth International Symposium on Epidemiology in Occupational Health. Como, Italy, September 1985.
14. Soskolne C, Jhangri G, Checkoway, Risch H, Siemiatycki J, et al. Sulphuric acid exposure in laryngeal cancer: induction and latency estimates from a lagged exposure window analysis. XII Scientific Meeting of the International Epidemiology Assoc. Los Angeles, August, 1990.
15. Payment P, Richardson L, Edwardes M, Franco E, Siemiatycki J. (1989). Gastrointestinal illness and drinking water: a prospective epidemiological study. 57th Conjoint Meeting on Infectious Diseases (CACMID), Montréal, 25-29 November 1989, Résumé C-30.
16. Payment P, Richardson L, Edwardes M, Franco E, Siemiatycki J. (1990). Drinking water related gastrointestinal illnesses. 1990 Annual Meeting of the American Society for Microbiology, Anaheim California, 13-17 May 1990.
17. Payment P, Richardson L, Edwardes M, Franco E, Siemiatycki J. (1990). A prospective epidemiological study of drinking water related gastrointestinal illnesses. International Association on water Pollution Research and Control, Health Related Water Microbiology Group, Tubingen, West Germany, 1-6 April 1990.
18. Case BA, Dufresne A, Siemiatycki J, Fraser R. Decoding occupational history from total lung particulate analysis. II: A comparative study. Brit. Occ. Hyg. Soc.; Seventh International Symposium on Inhaled Particles, Edinburgh, September 1991, S4.5.
19. Suarez-Almazor M, Soskolne C, Fung K, Jhangri G, Burch D, Howe G, Miller A, Siemiatycki J, Lakhani R, Dewar R. Choice of summary worklife exposure measures in the estimation of risk: an empirical assessment. Canadian Epidemiology Symposium. Edmonton. May. 1991.
20. Siemiatycki J, Nadon L, Dewar R. Cancer risks due to occupational exposure to polycyclic aromatic hydrocarbons. 8th International Symposium on Epidemiology in Occupational Health, Paris, France, September 1991.
21. Bourbonnais R, Siemiatycki J. Socioeconomic variables and cancer risk. Canadian Society for Epidemiology and Biostatistics. Edmonton, May 1991.
22. Gerin M, Begin D, Siemiatycki J, Dewar R. Study on the validity of the NOES job-exposure matrix using industrial hygiene measurements obtained in Montréal. Conference on Retrospective Assessment of Occupational Exposure. IARC Lyon. April 1994.
23. *Camus M, Siemiatycki J. Estimating past asbestos fiber levels in the general population of asbestos mining towns in Quebec. International Society Environmental Epidemiology, Research Triangle Park, N.C. Sept. 1994.
24. Goldberg MS, Dewar R, Siemiatycki J. Confounding and other design issues in cancer incidence studies of hazardous waste sites. Canadian Society for Epidemiology and Biostatistics. St-John’s, Newfoundland, Aug 1995.
25. Goldberg MS, Dewar R, Siemiatycki J. Confounding and other design issues in cancer incidence studies of hazardous waste sites. International Society for Environmental Epideemiology. Noordwijkerhout, Netherlands, Aug, 1995.
26. Case BW, Camus M, Siemiatycki J. Trends in Pathologic Diagnosis of Malignant Mesothelioma among Quebec Women 1970-1990. Royal College of Medicine. Montréal. Sept. 1995.
27. Aronson KJ, Siemiatycki J. Dewar R, Gerin M. Occupational Risk Factors for Prostate Cancer. Canadian Society for Epidemiology and Biostatistics, St-John’s, Newfoundland, Aug 1995.
28. *Camus M, Siemiatycki J. The Estimation of Past Asbestos Fiber Levels in Quebec Asbestos Mining Towns from 1900 to 1984. Canadian Society for Epidemiology & Biostatistics, St-John’s, Newfoundland, Aug 1995.

29. *Camus M, Siemiatycki J, Dewar R. Non-Occupational Asbestos Exposure and Risk of lung Cancer in the Female Population of Asbestos-Mining Towns: Implications for Risk Assessments. Canadian Society for Epidemiology and Biostatistics Meeting, St-John's, Newfoundland, Aug 1995.
30. Payment P, Franco E, Siemiatycki J, Richardson L, Renaud G, Prevost M. Epidemiology studies of tap-water related gastrointestinal illnesses. Water Quality Technology Conference, New Orleans, Nov. 1995.
31. *Fritschi L, Siemiatycki J. Self-assessed versus expert-assessed occupational exposures. Canadian Society for Epidemiology and Biostatistics Meeting, St Johns, Newfoundland, Aug 1995.
32. Payment P, Siemiatycki J, Richardson L, Renaud G. Épidémiologie des maladies gastro-intestinales et respiratoires: incidence, fraction attribuable à l'eau et coûts pour la société. ACFAS, Montréal, May 1996.
33. *Fritschi L, Parent M-É, Siemiatycki J. Gastric cancer and occupation. Australasian Epidemiological Association, Victoria, Australia. July 1996.
34. *Camus M, Case BW, Siemiatycki J. Risk assessment for women living in chrysotile mining towns.1: Environmental exposure assessment. Fourth International Mesothelioma Conference, Philadelphia, May 1997.
35. Case BW, Camus M, Siemiatycki J. Risk assessment for women living in chrysotile mining towns.2: Mesothelioma: observed vs. predicted. Fourth International Mesothelioma Conference, Philadelphia, May 1997.
36. *Camus M, Siemiatycki J. Cancer risks due to non-occupational asbestos exposure. Can. Soc. for Epidemiol. & Biostat. London, Ontario, May 1997.
37. Weston TL, Aronson KJ, Howe GR, Nadon L, Siemiatycki J. Cancer mortality risk in a cohort of working men. Canadian Society for Epidemiology and Biostatistics, London, Ontario, May 1997.
38. *Parent M-É, Siemiatycki J, Menzies L, Fritschi L, Colle E. Can Bacille-Calmette Guérin vaccination prevent insulin-dependent diabetes mellitus (IDDM)? Canadian Society for Epidemiology and Biostatistics, London, Ontario, May 1997.
39. Wolf, S, Siemiatycki J, Beyersmann, D, Jockel, K. H. A case-control study of lung cancer - performance of a job-exposure matrix for cadmium, chromium, nickel, and stainless steel dust. Internat. Epidemiol. Assoc. European Region Meeting. Munster, Germany, Sept. 1997.
40. *Parent, M.E. Siemiatycki J. Exposition professionnelle aux émissions d'essence et de diesel, et cancer du poumon. ACFAS, Quebec, May 1998.
41. *Parent M-É, Siemiatycki J, Boffetta P. Occupational exposure to gasoline and diesel engine emissions and lung cancer. Soc. Epid. Res, Chicago, June 1998.
42. *Parent M-É, Siemiatycki J, Boffetta P, Cohen A. Occupational exposure to gasoline and diesel exhausts and lung cancer. Inter. Soc. Environ. Epid, Boston, August 1998.
43. *Parent M-É, Siemiatycki J, Boffetta P, Cohen A. Gasoline and diesel engine emissions in the workplace and lung cancer. PREMUS-ISEOH '98, Helsinki, Finland, Sept. 1998.
44. Leffondre K, Abrahamowicz M, Rachet B, Siemiatycki J. Modeling smoking history: A comparison of different approaches. Congress of Epidemiology, Toronto, June 2001.
45. Fritschi L, Nadon L, Benke G, Lakhani R, Latreille B, Parent M-É, Siemiatycki J. Validation of expert assessment of occupational exposures X2001 – Occupational Exposure Assessment for Epidemiology and Practice, Gothenburg, Sweden, June 2001.
46. Parent M-É, Siemiatycki J, Desy M. Case-control study of occupational exposures and risk of prostate cancer among farmers. Case-control study of occupational exposures and risk of prostate cancer among farmers, Toronto, June 2001.
47. Siemiatycki J, Camus M, Parent M-É, Richardson L, Desy M, Case BW. Case-control study of pleural mesothelioma among women in Quebec chrysotile mining regions. Inhaled Particles IX (BOHS), Cambridge, United Kingdom, September 2001.
48. Jockel K-H, Wolf S, Ahrens W, Jahn I, Pohlabeln H, Beyersmann D, Siemiatycki J. Cadmium as a human lung carcinogen. Jahrestagung der Deutschen Arbeitsgemeinschaft fur Epidemiologie (DAE) [Annual convention of the German epidemiology working group], Garmisch-Partenkirchen, Germany, September 2001.

49. Leffondre K, Abrahamowicz M, Siemiatycki J. Comparison of Cox's model versus logistic regression for case-control data with time-varying exposure: a simulation study. Annual Meeting of the Statistical Society of Canada (SSC). Hamilton, Ontario. May 2002.
50. Parent M-É, Siemiatycki J, Desy M. Association between Alcohol Consumption and Each of 23 Types of Cancer in Men. Soc. Epid. Res, Palm Desert, California, June 2002.
51. Leffondre K, Abrahamowicz M, Siemiatycki J. Comparison of Cox's model versus logistic regression for case-control data with time-varying exposure: a simulation study. Society for Epidemiologic Research (SER), Palm Desert, California, June 2002.
52. Rachet B, Parent M-É, Siemiatycki J. Welding Fumes and Lung Cancer: A Case-Control Study, Soc. Epidemiol. Res, Palm Desert, California, June 2002.
53. Rachet B, Abrahamowicz M, Sasco A, Siemiatycki J. Flexible estimation of the distribution of lag in the effects of exposures and interventions. 34th Annual SER Meeting. Palm Desert, California. June 2002.
54. Abrahamowicz M, Mackenzie T, Leffondre K, Du Berger R, Siemiatycki J. Joint modeling of time-dependent and non-linear effects of continuous predictors in survival analysis, with application to re-assess the impact of intensity of past smoking on the risks of lung cancer in ex-smokers. 17th International Workshop on Statistical Modeling, Chania, Greece, July 2002.
55. Parent M-É, Siemiatycki J, Desy M. Exposure to chemical agents during leisure activities and risk of non-Hodgkin's lymphoma. Inter. Epidemiology Association, Montréal, August 2002.
56. Leffondre K, Abrahamowicz M, Siemiatycki J. Comparison of Cox's model versus logistic regression for case-control data with time-varying exposure: a simulation study. International Epidemiological Association (IEA), World Congress of Epidemiology, Montréal, Québec, August 2002
57. Rachet B, Siemiatycki J, Leffondre K, Abrahamowicz M. Exposure-response relationships between cigarette smoking and male lung cancer from a case-control study in Montréal: generalized additive model approach. International Epidemiology Association (IEA) XVI World Congress of Epidemiology. Montréal, Québec. August 2002.
58. Parent M-É, Rousseau M-C, Siemiatycki J, Desy M. Body mass index and male cancer incidence at twelve different sites. Body mass index and male cancer incidence at twelve different sites. Halifax, Nova Scotia, June 2003.
59. Desautels N, Siemiatycki J, Parent M.E. Association between lifetime consumption of coffee, tea, and soft drinks, and incidence of eleven types of cancer: a case-control study. CSEB 2003 Biennial Meeting. Halifax, Nova Scotia, June 2003.
60. Parent M-É, Siemiatycki J, Desy M. Association between beta-carotene intake and risk of cancer at several sites. Society for Epidemiologic Research, Atlanta, Georgia, June 2003.
61. Parent M-É, Siemiatycki J, Laplante O, Desy M. Risk of lung cancer and mesothelioma associated with occupational exposure to Asbestos: A population-based case-control study in Montréal, Canada. International Society for Environmental Epidemiology, Perth, Australia, September 2003.
62. Parent M-É, Siemiatycki J, Laplante O, Désy M. Occupational exposure to asbestos and risk of lung cancer and mesothelioma: results from a population-based-case-control study in Montréal. CARWH Conference. Montréal, Québec, October 2003.
63. Parent M-É, Siemiatycki J, Latreille B, Désy M. Lifetime Occupational Physical Activity and Prostate Cancer Risk. Society for Epidemiologic Research. Salt Lake City, Utah, June 2004.
64. Parent M-É, Rousseau M.C, Siemiatycki J, Boffetta P, Cohen A. Contrasting evidence when using hospital or population controls: the example of the association between exposure to gasoline and diesel exhaust, and lung cancer. 16th conference of the International Society for Environmental Epidemiology (ISEE). New York City, August 2004.
65. De Guire L, Lebel G, Gingras S, Levesque B, Camus M, Provencher S, Case B, Langlois A, Laplante O, Siemiatycki J, Lajoie P. Epidemiology of Asbestos-related diseases in Québec, Canada. EPICOH 2004. Melbourne, Australia, October 2004.
66. Richardson H, Aronson K, Parent M-É, Siemiatycki J. Risk of cancer due to occupational exposure to six types of chlorinated hydrocarbons. EPICOH, Melbourne, Australia, October 2004.

67. De Guire L, Lebel G, Gingras S, Levesque B, Camus M, Provencher S, Case B, Langlois A, Laplante O, Siemiatycki J, Lajoie P. Épidémiologie des maladies reliées à l'exposition à l'amiante au Québec. Board Meeting, Canadian Association of University Teachers. Ottawa, November 2004.
68. Rousseau M-C, Parent M-É, Siemiatycki J. Occupational exposure to lead and risk of cancer in a population-based case-control study from Montréal, Canada. Canadian Association for Research on Work and Health, Vancouver, May 2005.
69. Parent M-É, Rousseau M-C, Siemiatycki J, Desy, M. Using proxy respondents when assessing occupational circumstances in a case-control study of cancer: For better or for worse? Canadian Association for Research on Work and Health, Vancouver, May 2005.
70. *Momoli F, Siemiatycki J, Parent M-É, Abrahamowicz M. Semi-Bayes modeling in a study of lung cancer and multiple occupational chemicals: Comparison of results for five suspected lung carcinogens. Canadian Association for Research on Work and Health, Vancouver, May 2005.
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107. Olsson A.C., Gustavsson P, Kromhout H, Siemiatycki J, et al. Pooled Analyses on Diesel Motor Exhaust and Lung Cancer in Europe and Canada. Poster presentation. 29th ICOH International Congress on Occupational Health, Cape Town, South Africa, March 2009.
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110. Nkosi MT, Rousseau M-C, Parent M-É, Siemiatycki J. Studying socio-economic status and lung cancer risk; How important Is the modelling of smoking? Poster presentation at the Canadian Society for Epidemiology and Biostatistics (CSEB) Student Conference, Ottawa Ont, May 2009.
111. Rousseau M-C Parent M-E, Nicolau B, Koushik A, Siemiatycki J. Body mass index and lung cancer risk in a population-based case-control study from Montréal, Canada. Poster presentation at the 42nd Annual Meeting of the Society for Epidemiological Research (SER) Meeting Anaheim Ca, June 23-26 2009.
112. *Pintos J, Parent M-E, Siemiatycki J. Occupational exposure to diesel engine emissions and risk of lung cancer; evidence from case-control study in Montréal. Oral presentation. 42nd Annual Meeting of the Society for Epidemiologic Research Meeting (SER), Anaheim, June 23-26 2009.
113. *Perron S, Jacques L, Siemiatycki J, Ducharme F. Home multifaceted environmental interventions to improve asthma control: A systematic review. 137th Annual Meeting of the American Public Health Association (APHA), November 7-11 2009, Philadelphia, PA.
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121. *Liu A, Abrahamowicz M, Siemiatycki J. Methodological challenges in testing and estimating interactions with multi-dimensional exposures. Annual Meeting of the Society for Epidemiologic Research (SER), Seattle, June 2010.
122. Rousseau M-C, Conus F, Parent M-É, Siemiatycki J. History of allergic diseases and risk of lung cancer. Poster présentation. Third North American Congress of Epidemiology, Montréal, June 2011. Am. J. Epidemiol. (2011) 173 (suppl 11):S29.
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132. Siemiatycki J, Richardson L, Kincl L, Schlaefer K, Cardis E. Oral presentation. INTEROCC Study: Social Class and The Risk of Glioma Brain Tumours. International Society for Environmental Epidemiology (ISEE), Barcelona, Spain, September 2011.

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134. Kendzia B, Pesch B, Jöckel K.-H, Kromhout H, Straif K, Brüning T, on behalf of the SYNERGY Working Group. Lung cancer risks of welding in a pooled analysis of case-control studies. Oral presentation. 7th International Conference on Science of Exposure Assessment (X2012), Edinburg, Scotland, July 2012.
135. Olsson A.C, Vlaanderen J, Vermeulen R, Kromhout H, Pesch B, Straif Kurt on behalf of the SYNERGY study Group. Improved risk estimation through advanced exposure modelling in community-based studies: the example of occupational asbestos exposure in the SYNERGY project. Oral presentation. 7th International Conference on Science of Exposure Assessment (X2012), Edinburgh, Scotland, July 2012.
136. *Lacourt A, Lavoué J, Labrèche F, Siemiatycki J. Gender differences in occupational exposures assessed by experts in a community based-case control study of lung cancer. Oral presentation 7th International Conference on the Science of Exposure (X2012), Edinburgh, Scotland, July 2012.
137. *Pasquet R, Karp I, Siemiatyck J, Koushik A. Intake of black tea and coffee and the risk of lung cancer. E-poster. UICC World Cancer Congress, Montréal, Quebec, 27-30 August 2012.
138. *Vallières E, Siemiatycki J, Lavoué J, Pintos J, Parent M-E. Risk of three histological types of lung cancer after exposure to welding fumes. Poster presentation, UICC World Cancer Congress, Montréal, Quebec, 27-30 August 2012.
139. *Rivera M, *Vizcaya D, Pintos J, Abrahamowics M, Siemiatycki J. Association between exposure to engine emissions and lung cancer. 23rd International Conference on Epidemiology in Occupational Health (EPICOH), Utrecht, Netherlands, 18-21 June 2013.
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142. Turner M-C, Benke G, Bowman J, et al. Occupational exposure to extremely low frequency magnetic fields and brain tumour risks in the INTEROCC study. Environment and Health – Joint meeting of the International Society for Environmental Epidemiology (ISEE), the International Society for Exposure Sciences (ISES) and the International Society for Indoor Air Quality (ISIAQ), Basel, Switzerland, 19-23 August 2013.
143. Lavoué J, Labrèche F, Richardson L, Goldberg M, Parent M-E, Siemiatycki J. CANJEM: a general population job exposure matrix based on past expert assessments of exposure to over 250 agents. 24th International Conference on Epidemiology in Occupational Health (EPICOH), Chicago, Illinois, 24-27 June 2014. [abstract] Occupational & Environmental Medicine. 2014;71 (Suppl 1):A48.
144. *Ho V, Parent M-E, Pintos J, Abrahamowicz M, Gauvin L. Siemiatycki J, Koushik A. Lifetime occupational physical activity and lung cancer risk. 17ème Congrès des étudiants, stagiaires et résidents du CRCHUM, Montréal, Quebec, December 2014.
145. Turner M C, Sadetzki S, Eastman Langer C, Figuerola J, Armstrong BK, Chetrit A, Giles GG, Krewski D, Hours M, McBride /ML, Parent M-E, Richardson L, Siemiatycki J, Woodward A, Cardis E. Impact of case:control matching strategies on associations between cellular telephone use and glioma risk in the INTERPHONE study. International Society for Environmental Epidemiology (ISEE), Seattle, Washington, 25 August 2014.
146. *Dutczak H, Siemiatycki J, Koushik A. Exposure to stressful life events and lung cancer risk. 10ème Colloque Annuel de l'Association des Étudiantes et Étudiant en Santé Publique de l'Université de Montréal, Quebec, February 2015.
147. *Xu M, Richardson L, Campbell S, Siemiatycki J. Trends and Characteristics of Response Rates in Case-Control Studies of Cancer. 10ème Colloque Annuel de l'Association des Étudiantes et Étudiant en Santé Publique de l'Université de Montréal, Montréal, Quebec, February 2015.

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150. *Pasquet R, Cardis E, Richardson L, Lavoué J, Siemiatycki J, Koushik A. The association between occupational exposure to metals and metalloids and brain cancer risk. Canadian Society for Epidemiology and Biosatistics (CSEB), Mississauga, Ontario, 1-4 June 2015.
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152. Behrens T, Groß I, Siemiatycki J, Conway D, Jöckel K-H, Olsson A, Kromhout H, Straif K, Schüz J, Hovanec J, Kendzia B, Pesch B, Brüning T. Niedriges berufliches Prestige, soziale Mobilität und Lungenkrebs – die SYNERGY-Studie. German Epidemiology Association (DGEpi), Potsdam, Germany, September 2015.
153. *Carrier M, Kestens Y, Siemiatycki J. Nuisances environnementales et risques pour la santé. AQTR, Montréal, Quebec, 15 September 2015.
154. *Sauvé JF, Siemiatycki J, Labrèche F, Lavoué J. Development of the CANJEM job exposure matrix: Bayesian modelling of occupational exposures assigned by experts to over 30000 jobs spanning 1920-2005. The International Society of Exposure Science (ISES), Henderson, Nevada, 18-22 October 2015.
155. Vila J, Bowman JD, Richardson L, Kincl L, Conover D, van Tongeren M, Mann S, Vecchia P, McLean D, Cardis E, on behalf of the INTEROCC Study Group. Assessing cumulative exposures to electromagnetic fields: From source-based measurements to individual lifetime exposure estimates. The International Society of Exposure Science (ISES) Henderson, Nevada, 18-22 October 2015.
156. *Karumanchi S, Hatsopoulou M, Richardson L, Siemiatycki J. Methodology for exposure assessment for UFPs in the Grand Montréal Region. Oral presentation. 11th Annual Symposium of the Student Association in Public Health at the Université de Montréal (AÉÉSPUM), Montréal, Quebec, 9 February 2016.
157. *Carrier M, Apparicio P, Kestens Y, Séguin AM, Pham H, Crouse D, Siemiatycki J. Application of a global environmental equity index in Montréal: diagnostic and further implications, AAG, San Francisco, California, 30 March 2016.
158. *Carrier M, Apparicio P, Kestens Y, Séguin A-M, Pham H, Crouse D, Siemiatycki J. Application d'un indice d'équité environnementale à Montréal: établissement d'un diagnostic pour cibler les secteurs et les groupes les plus vulnérables, ACFAS, Montréal, Quebec, 11 May 2016.
159. *Carrier M, Kestens Y, Crouse D, Siemiatycki J. Lung cancer and exposure to Nitrogen Dioxide and Traffic in Montréal, World Conference on Transport Research, Shanghai, China, 10 July 2016.
160. *Xu M, Richardson L, Campbell S, Pintos J, Siemiatycki J. Patterns and trends in quality of response rate reporting in case-control studies of cancer. 18th Congress of Students, Interns and Residents of CRCHUM, Montréal, Quebec, 4 May 2016.
161. *Xu M, Richardson L, Campbell S, Pintos J, Siemiatycki J. Time trends and study design determinants of response rates in case-control studies of cancer. 18th Congress of Students, Interns and Residents of CRCHUM, Montréal, Quebec, 4 May 2016.
162. *Karumanchi S, Hatsopoulou M, Richardson L, Thierry B, Goldberg M, Siemiatycki J. Land use regression model of UFPs in the Grand Montréal Region. Oral presentation. Canadian Society for Epidemiology and Biostatistics, Winnipeg, Manitoba, 8-10 June 2016.
163. *Xu M, Richardson L, Campbell S, Pintos J, Siemiatycki J. Subject response rates in case-control studies of cancer: quality of reporting, time trends, and study design determinants. Epidemiology Congress of the Americas, Miami, Florida, 21-24 June 2016.
164. *Rémen T, Siemiatycki J, Lavoué J. Impact of inter-coder differences in occupation and industry classification coding on exposure estimates obtained via job-exposure matrix: example of gasoline engine

emissions in CANJEM. Oral presentation. 25th EPICOH - Epidemiology in Occupation Health Conference, Barcelona, Spain, 4-7 September 2016.

165. *Sauvé JF, Lavoué J, Siemiatycki J, Parent ME. Evaluation of a hybrid expert approach for retrospective assessment of occupational exposures in a population-based study of prostate cancer in Montréal, Canada. Oral presentation. 25th EPICOH - Epidemiology in Occupation Health Conference, Barcelona, Spain, 4-7 September 2016.
166. *Pasquet R, Cardis E, Richardson L, Lavoué J, Siemiatycki J, Koushik A. The association between occupational exposure to metals and metalloids and brain cancer risk. 25th EPICOH - Epidemiology in Occupation Health Conference, Barcelona, Spain, 4-7 September 2016.
167. Russ D, Rémen T, Ho KY, Chow WH, Davis F, Hofmann J, Huang H, Purdue M, Schwartz K, Siemiatycki J, Zhang Y, Silverman D, Johnson C, Lavoué J, Friesen M. Recommendations for prioritizing expert review of free-text job descriptions that underwent computer-based coding using the SOCcer algorithm. 25th EPICOH - Epidemiology in Occupation Health Conference, Barcelona, Spain, 4-7 September 2016.
168. *Sauvé JF, Labrèche F, Richardson L, Goldberg MS, Parent MÉ, Siemiatycki J, Lavoué J. Development of the CANJEM Canadian general-population job-exposure matrix from past expert evaluations. Oral presentation. Canadian Association for Research on Work and Health (CARWH) conference, Toronto, Ontario, October 2016.
169. *Rémen T, Siemiatycki J, Lavoué J, Verner MA. Impact of inter-coder differences in occupation and industry classification coding on exposure estimates obtained via job-exposure matrix: example of gasoline engine emissions in CANJEM. Poster. International Society of Exposure Science (ISES) 2016 Annual Meeting, Utrecht, Netherlands, 9-13 October 2016.
170. Grundy A, Ho V, Parent ME, Siemiatycki J, Koushik A. Lifetime recreational moderate-to vigorous physical activity and the risk of ovarian cancer by subtype. Poster presentation. 2016 American Institute for Cancer Research (AICR) Research Conference, North Bethesda, Maryland,14-16 November 2016.
171. Grundy A, Ho V, Parent ME, Siematycki J, Koushik A. The impact of menopausal status on the association between moderate-to-vigorous physical activity among participants in the Prevention of OVArian Cancer in Quebec (PROVAQ) study. Oral Presentation. Canadian Society for Epidemiology and Biostatistics 2017 Biennal Conference, Banff, Alberta, 1 June 2017
172. Bowman JD, Vila J, Richardson L, Kincl L, Cardis E on behalf of the INTEROCC Study Group. Occupational Exposures to Radio-frequency Electric Fields Assessed for the INTEROCC Study of Brain Cancer. Oral presentation. American Industrial Hygiene Association conference, Seattle, Washington, 4-7 June 2017.
173. *Karumanchi S, Siemiatycki J, Hatzopoulou M. Some challenges in measuring ultra-fine particles and developing a land use regression model. Oral presentation. Canadian Society for Epidemiology and Biostatistics (CSEB) 2017 Biennal Conference, Banff, Alberta, 30 May 2017.
174. *Sauvé JF, Davies HW, Parent MÉ, Peters CE, Siemiatycki J, Sylvestre MP, Lavoué J. Development of quantitative estimates of wood dust exposure in a Canadian general population job-exposure matrix based on past expert assessments. 26th Conference on Epidemiology in Occupational Health (EPICOH 2017), Edinburgh, Scotland, August 2017.
175. Ho V, Xu M, Pintos J, Lavoué J, Abrahamowicz M, Rousseau M.C, Richardson L, Siemiatycki J. Occupational exposures to leaded and unleaded gasoline engine emissions and lung cancer risk. Canadian Cancer Research Conference, Vancouver, British Columbia, 5-7 November 2017.
176. Lequy E, Siemiatycki J, Leblond S, et al. Moss biomonitoring as an alternative to assess exposure to atmospheric metals in environmental epidemiology: the example of the bramm network and the gazel cohort. Poster. SEE Young 2018, Early Career Researchers Conference on Environmental Epidemiology – Together for a Healthy Environment, Freising, Germany, 19–20 March 2018. Occup Environ Med 2018;75:A27.
177. Ho V, Parent MÉ, Lavoué J, Zhu Y, Siemiatycki J, Koushik A. Gender Differences in Occupational Physical Activity. Oral presentation. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario. 26-30 August 2018.

178. *Xu M, Ho V, Siemiatycki J. Association between occupational exposure to textile fibre dusts and lung cancer in a population-based case-control study in Montréal: a preliminary analysis comparing results from three analytical methods. Oral presentation. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.
179. Zhu Y, Lavoué J, Parent MÉ, Siemiatcyki J, Koushik A, Ho V. Occupational Physical Activity and Lung Cancer Risk among Participants of the Alberta's Tomorrow Project. Poster. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.
180. *Karumanchi S, Siemiatycki J, Richardson L, Hatzopoulou M. Estimating exposure to Ultrafine Particles in the Greater Montreal Area among case-control study subjects: Comparison of classical land use regression model with a model based on Bayesian principles - Proposal. Poster. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.
181. van Tongeren M, Dirkx E, Lavoué J, Siemiatycki J, Ho V. Assessment of Occupational Exposure to Endocrine Disrupting Agents. Poster. ISES-ISEE 2018 Joint Annual Meeting, Ottawa, Ontario, 26-30 August 2018.

* First author was under supervision of J. Siemiatycki when this work was carried out

GRANTS AND CONTRACTS RECEIVED

1. Comparison of three methods for conducting household health surveys; Nat. Health Res & Devel. Prog. (NHRDP); $27,000; 1974-76.
2. Pilot study of a case-control monitoring system for discovering occupational carcinogens; Conseil de la recherche en santé (CRSQ); $80,000; 1978-1980.
3. Établissement du jeune chercheur; CRSQ; $15,000; 1979-80.
4. Analyse de santé auprès de 1600 ménages montréalais; Ministère des affaires sociales (MAS); $12,708; 1980
5. Dépistage des facteurs cancérigènes de l'environnement professionnel montréalais: étude pilote; Commission des accidents du travail; $59,093 ; 1980-82.
6. Registry of patients with Juvenile Onset Diabetes in Québec; NHRDP; $35,478*; 1980-85; (P.I. Dr E. Colle).
7. Secondary analysis of a health survey in Montréal: methodologic issues and comparison of morbidity and health care utilization between social groups; NHRDP-H&W Can.; $15,000; 1981-82.
8. Exposure-based case-control approach to discovering occupational carcinogens; NHRDP-H&W Can.; $129,258; 1981-83.
9. An exposure-based case-control approach to discovering occupational carcinogens; NCIC; $131,842; 1981-83.
10. Variation in sex ratios of cancer between geographic areas; NCIC; $3,227; 1982-84.
11. Équipe associée en épidémiologie des cancers professionnels (Team grant); Institut de la recherche en santé et sécurité du travail (IRSST); $1 120,000; 1982-85.
12. Formaldehyde et cancer; IRSST; $9,500; 1983.
13. Retrospective cohort study in the Montréal fur industry; IRSST; $34,019; 1983-85.
14. Statistical analysis of a case-control study designed to discover occupational carcinogens; NHRDP-H&W Can.; $484,022; 1985-87.
15. Completion of chemical coding of exposures in a case-control study designed to discover occupational carcinogens; IRSST; $102,180; 1986.
16. Risks of cancer due to exposure to asbestos in a range of occupations; IRDA; $61,206; 1986-87.
17. Biological estimation of exposure: a tissue registry for the identification and quantification of occupational carcinogens; NCIC; $3,500*; 1986-87; (P.I. Dr B. Case)
18. Development of a proposal to study cancer risk and non-occupational exposure to asbestos; H&W Can.; $29,500; 1987-88.
19. Evaluation of cancer risk and occupational exposure to formaldehyde; H&W Can.; $30,000; 1987-88.
20. A genetic-epidemiologic study of breast cancer; NIH-NCI; $90,945(US)*; 1987-92; (P.I. Dr. R. Haile).

21. Scholar award; NHRDP-H&W Can.; $298,689; 1987-93.
22. An intervention trial to assess the risks of gastro-intestinal illness associated with consumption of treated tap water; NHRDP; $225,000*; 1987-89; (P.I. Dr P. Payment).
23. Evaluation of cancer risk and occupational exposure to polycyclic aromatic hydrocarbons; H&W Can.; $29,500; 1988-89.
24. Evaluation of cancer risk and occupational exposure to benzene, toluene and xylene; H&W Can, $40,000; 1988-89.
25. Health risks due to chrysotile asbestos in the non-occupational environment: a workshop to evaluate a research protocol; H&W Can, $20,000; 1988-89.
26. A population-based, case-control study of occupational exposure to sulphuric acid and the development of laryngeal cancer: an augmented secondary data analysis; NHRDP; $11,120*; 1988-89; (P.I. Dr. C. Soskolne).
27. Mortality due to asbestos in the general environment of the Quebec mining areas; H&W Can.; $130,000; 1989-90.
28. A case-control approach to discovering occupational carcinogens: an analysis of data; NHRDP; $55,508; 1989-90.
29. Continued analysis of a large case control study of many types of cancer: occupational and non-occupational risk factors; NHRDP; $463,827 1988-1992
30. Risk of cancer due to cigarette smoking - results of a multi-site case-control study; H&W Can.; $30,000; 1989-90.
31. Étude sur la validité de matrice emploi-expositions multisectorielles; IRSST; $18,207*; 1990-1992; (P.I. Dr. M. Gérin).
32. Équipe en épidémiologie environnementale (Team grant in environmental epidemiology) ; Fonds de recherche en santé du Québec; $526,297; 1990-1994.
33. Leukemia in children due to parental occupational exposures; NHRDP; $108,000*; 1990-1994; (P.I. Dr Claire Infante-Rivard).
34. Risk of cancer due to exposure to chlorinated solvents - results of a multi-site case-control study; H & W Can.; $30,000; 1991-92.
35. Non-occupational exposure to Quebec chrysotile asbestos and risk of cancer retrospective assessment of exposure; H & W Can.; $60,000; 1991-92.
36. Feasibility of epidemiologic methods to investigate health outcomes near waste sites; H & W Canada; $33,000; 1991-92
37. A pilot study to evaluate the prevalence of hip arthritis in the Montréal urban setting, and an evaluation of methods of recruitment of a population aged 65+; Montréal General Hospital Clinical Epidemiology; $15,000*; 1991-92; (P.I. Dr. J. Esdaile).
38. Non-occupational exposure to Quebec chrysotile asbestos and risk of cancer; mesothelioma ascertainment; NHRDP; $164,000; 1991-95.
39. Multivariate Regression Analyses of Occupational Risk Factors for Several Types of Cancers; NHRDP; $128,827; 1992-96.
40. Development of a Job-Exposure Matrix for Use in Epidemiologic Case-Control Studies of Occupational Risk Factors; NHRDP; $85,003; 1992-95.
41. A prospective epidemiological study of gastrointestinal health effects due to consumption of drinking water. E.P.A. (US)/ NHRDP/ Nat. Water Res. Inst.; $300,000*; 1993-95. (P.I.: Dr. P. Payment)
42. A population-based, case-control study of occupational exposure to acidifying agents and the development of lung cancer: an augmented, secondary data analysis. NHRDP; $72,220*; 1993-1995. (P.I. Dr. C. Soskolne).
43. Scholar award; NHRDP-Health Canada; $126,990; 1993-95.
44. Équipe en épidemiologie environnementale (Team grant in environmental epidemiology) ; Fonds de recherche en santé du Québec; $242,652; 1994-1998.
45. Examen pathologique de cas présumés de mésothéliome recensés chez des femmes depuis 1970 dans des hôpitaux du québec. Health and Welfare Canada. $30,000. 1994.

46. Cohort Study of a Ten Percent Sample of the Canadian Labour Force. NHRDP; $12,000*; 1994-97. (P.I. Dr. K. Aronson)
47. A health survey of persons living near the Miron Quarry Sanitary Landfill site, Montréal: a pilot study. NHRDP; $88,931 ; 1994-95. (P.I. Dr. M. Goldberg)
48. Occurrence of pathogenic microorganisms in water from St Laurent hydrological basin. FRSQ/ NHRDP & St Laurent Vision 2000; 1995-97. (P.I. P Payment)
49. Case-control study of lung cancer and environmental tobacco smoke; Health Canada; $544,344; 1995-1997.
50. Case-control study of lung cancer and occupational exposures: NHRDP; $840,000.; 1995–1998.
51. Occupational exposure to solvents and risk of breast cancer; National Cancer Institute of Canada; $300,000*; 1995-1997. (P.I.: M Goldberg).
52. Scholar Award; NHRDP-Health Canada; $263,329, 1995-1998.
53. Reanalysis of US data relating general mortality to air pollution; Health Effects Institute; 1998-2000 (P.I. D Krewski)
54. A case-control study of occupational risk factors for lung cancer; Medical Research Council of Canada; $554,757, 1998-2001
55. Évaluation du risque de cancer du poumon et de mésothéliome associé à l'exposition à l'amiante chez les travailleurs de la région montréalaise; Ministère de la Santé et des Services sociaux; $12,000. 1998.
56. Feasibility of a case-control study of the association between cell phone use and brain, salivary gland cancer and acoustic neurinoma. International Agency for Research on Cancer; $12,000, 1998.
57. Inorganic particulate retained dose markers in lung cancer and mesothelioma. CIHR (P.I. Bruce Case) $66,096. 1999-2003
58. Distinguished Scientist Award, Medical Research Council of Canada; $330,000; 1999-2004.
59. Évaluation du risque de mésothéliome associé à l'exposition à l'amiante chez les femmes de la région minière; Ministère de la Santé et des Services sociaux; $27,500. 1999-2000.
60. Program of research in environmental epidemiology of cancer (a national program to enhance capacity to conduct research) PREECAN; National Cancer Inst of Canada; $1,000,000; 2000-2004.
61. Designing a national research agenda in environmental epidemiology of cancer. Medical Research Council of Canada Opportunities Program; $40,000; 2000-2001.
62. Multi-centric case-control study of cell phone use and cancer risk in Montréal. CIHR; $500,000; 2000-2004.
63. Trainee award for: Bernard Rachet, Post-doctoral fellow. PREECAN – NCIC; $46,750; 2001-2003.
64. Cardiogene: a consortium to explore the gene-environment paradigm of major cardiovascular disorders in human and animal models. Canadian Institutes of Health Research, (P.I. P. Hamet) $2,632,272; 2001-2007.
65. Canada Research Chair in Environmental Epidemiology. Federal CRC program. $1,400,000; 2001-2008.
66. Installation of CRC. Canadian Foundation for Innovation. $312,000; 2002-2004.
67. Occupational and lifestyle factors in the etiology of prostate cancer, and establishing a platform for studying susceptibility biomarkers (Part 1). Canadian Cancer Society, Prostate Cancer Research Initiative, National Cancer Institute of Canada, (P.I. M-É Parent) $947,360; 2002-2007.
68. Center for research on environmental etiology of cancer. For the application process. Centre Hospitalier de l'Université de Montréal (CHUM); $7,000; 2002-2003.
69. Traffic-related air pollution and socioeconomic gradients in the incidence of cancer. CIHR, (P.I. M Goldberg) $497,000; 2004-2007.
70. Development and validation of new statistical methods for modeling intermediate events in survival analysis. CIHR, (P.I. M Abrahamowicz) $68,250; 2004-2005.
71. New survival analytic methods for time-dependent exposures in case-control studies, with applications to cancer. CIHR (P.I. K Leffondré) $52,791; 2004-2007.
72. Trainee award for: Venkata Ramana Kumar, Post-doctoral fellow. PREECAN – NCIC; $66,000; 2004-2007.

73. Environmental Cancer Research Team. Development grant for the preparation of the full team grant application. CIHR (P.I. J. Siemiatycki) $9,500; 2005-2006.
74. Trainee award for: Franco Momoli, PhD student. PREECAN – NCIC; $25,600; 2005-2006.
75. Occupational and selected non-occupational risk factors for lung cancer: Analysis of a case-control study in Montréal. CIHR (co-P.I.'s: J Siemiatycki & M-É Parent) $1,920,447; 1999.2011.
76. Development and evaluation of a cost-effective approach for retrospective assessment of occupational exposures in population-based studies (pilot study). Canadian Cancer Etiology Research Network - NCIC (P.I. M-É Parent) $35,000; 2006-2007.
77. Trainee award for: Aihua Liu, PhD student. PREECAN – NCIC; $12,600; 2006-2007.
78. Prostate cancer and occupational whole body vibration. Ontario Workplace Insurance Board: Research Advisory Council; Solutions for Workplace Change (P.I. J Purdham); $140,480; 2006-2008.
79. Guzzo-SRC Chair in Environment and Cancer. Cancer Research Society, $1,285,000; 2007-2020.
80. INTEROCC: Occupational exposures and brain cancer. NIH (P.I. E Cardis: To support the analysis of the occupational component of an international case-control study involving 13 countries and coordinated at the International Agency for Research on Cancer of the WHO [France]); $1,626,757 US; 2008-2010.
81. Development and validation of a lung cancer risk prediction model. NCIC (P.I. I Karp); $102,099; 2008-2010.
82. Occupational and lifestyle factors in the etiology of prostate cancer, and establishing a platform for studying susceptibility biomarkers (Part 2). NCIC (P.I.: M-É Parent); $756,000; 2008-2011.
83. Preparation and development of an epidemiological study of modifiable and genetic factors associated with ovarian cancer risk (pilot project). Ovarian Cancer Canada (P.I.: A Koushik); $28,330; 2008-2009.
84. SYNERGY - Pooled analysis of case-control studies on the joint effects of occupational carcinogens in the development of lung cancer: Montréal component. German Statutory Accident Insurance (DGUV) (P.I.: A Koushik); $119,177; 2008-2010.
85. The risk of lung cancer related to occupational and recreation physical activity and to dietary intake of flavonoids. Canadian Cancer Research Society. (P.I.: A Koushik); $208,317; 2009-2012.
86. A case-control study of modifiable and genetic factors associated with the risk of ovarian cancer. Canadian Cancer Society Research Institute (P.I: A Koushik); $498,997; 2010- 2013.
87. Occupational and selected nonoccupational risk factors for lung cancer: analysis of a case-control study in Montréal. CIHR (P.I: J Siemiatycki, M-É Parent); $850,620; 2011-2015.
88. Quebec Research Program for Prostate Cancer Prevention. Cancer Research Society (P.I.: M-É. Parent, P Karakiewics) $4,728,203; 2011-2015.
89. Extreme weather and maternal-child health: targeting future impacts of climate change. CIHR. (P.I.: N Auger) $85,333; 2015-2019.
90. Development of an instrument for assessing occupational exposures in cancer case-control studies and its application to cancers of lung, brain, ovary. Cancer Research Society- Programme GRePEC (Groupe de recherche et de prévention en environnement-cancer). (P.I.: J Siemiatycki, M Pollak) $2,510,890; 2011-2018.
91. Occupational physical activity and lung cancer. (P.I.: V Ho, A Koushik).CIHR. $75,000. 2017-2018.
92. Analyses of existing Canadian cohorts and databases related to occupational physical activity and lung cancer risk. CIHR. (P.I.: V Ho, A Koushik) $74,989; 2017-2018.
93. The role of lifestyle factors in ovarian cancer prognosis. Department of Defence – Ovarian Cancer Research Program. (P.I.: A Koushik) $216,458 USD (est. $293, 000 CAD); 2015-2017. Extended August 2018.
94. Occupational Exposure to Endocrine Disrupting Chemicals and Colorectal Cancer risk. CIHR (P.I.: V Ho, J Siemiatycki) $252,450; 2018-2021.
95. Occupational exposures of women: improvement of an existing job exposure matrix to provide gender-specific estimations of exposure. IRSST. (P.I.: V Ho) $491,484; 2018-2021.

Exhibit 27

Hysterosalpingo-Radionuclide Scintigraphy (HERS)

Mario Iturralde and Pieter Ferdinand Venter

A radionuclide procedure, hysterosalpingo-radionuclide scintigraphy (HERS), was designed to evaluate the migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries as well as to image and functionally outline the patency of the pathways between these two extremes of the female reproductive system. Technetium-99m human albumin microspheres (^{99m}Tc-HAM) were deposited in the posterior fornices of patients who were divided into two specific groups. Group I consisted of patients who were to undergo different elective gynecologic operations, in which besides obtaining sequential images, radioactivity levels were measured in the removed organs and tissues. Group II consisted of patients referred by the Infertility Clinic for evaluation of their reproductive system pathways patency. In this latter group, HERS was compared with contrast hysterosalpingography (HSG) and peritoneoscopy (PCP). The results obtained from measurements of radioactivity levels on the removed surgical specimens and comparison with other conventional gynecologic diagnostic procedures provide accurate evidence of the migration of ^{99m}Tc-HAM from the vagina, through the uterus and tubes, to the peritoneal cavity and ovaries, and show that HERS is a simple noninvasive method for functionally imaging and assessing the patency of the female reproductive system pathways.

IN THE adult female, the peritoneal cavity communicates with the outside via the fallopian tubes, the uterus, and the vagina and there is evidence for the migration of different substances in either direction (Fig. 1). For example, malignant cells from ovarian carcinoma can be demonstrated in the posterior fornix of the vagina.[1] After menstruation, the gonococcus can penetrate the cervix and gain access through the uterus and tubes to the peritoneal cavity and ovaries.[2] Retrograde menstruation is also a well known phenomenon. For pregnancy to occur, spermatozoa have to move up the uterus as the ova moves down the tube. After insufflation, air and gases pass easily from the vagina into the peritoneal cavity up to the diaphragm. Radioopaque contrast media are introduced with great ease through the uterus and tubes into the peritoneal cavity, and tubal patency is easily demonstrated during peritoneoscopy by injection of a dye through the cervix and into the tubes.

If transit can take place so easily, it is probable that the same happens with chemical substances used for hygienic, cosmetic, or medicinal purposes, many of which may have potential carcinogenic or irritating properties (Table 1). Such migration could well explain the etiologic role of chemical substances in certain gynecologic diseases, and specially in carcinoma of the ovary.[3-5] A role for environmental factors and socioeconomical conditions in the origin of ovarian carcinoma has been inferred from its higher incidence in industrialized countries[6] (Table 2). The incidence of carcinoma of the ovaries in South African whites is substantially higher than in South African blacks.[5]

The products of industry upon which most attention has been focused are asbestos and talc. Whereas the carcinogenic properties of asbestos are undisputed,[7] there is still controversy over talc.[8] Although conclusive data are lacking, various facts indicate that talc could be a possible carcinogen, cocarcinogen, or promoter of malignant transformation, and should not be used as a dusting powder.[9] This is based on the fact that talc, a hydrous magnesium silicate [$Mg_6S_{18}O_{20}(OH)_4$] is chemically similar to asbestos, which is a calcium magnesium silicate [$Ca_2MG_5S_{18}O_{22}(OH)_2$]; besides, talc frequently contains microscopic fibers of asbestos as a contaminant.[10]

Access of talc to the peritoneal cavity is most likely through the vagina. Studies of the transport of particles in the human female reproductive tract have shown that nonmotile inert carbon particles deposited in the vagina can be recovered 30–35 min later in the fallopian tubes.[11]

Electron micrographic slides of removed human ovaries have shown asbestos particles resting on them, and there is evidence that these

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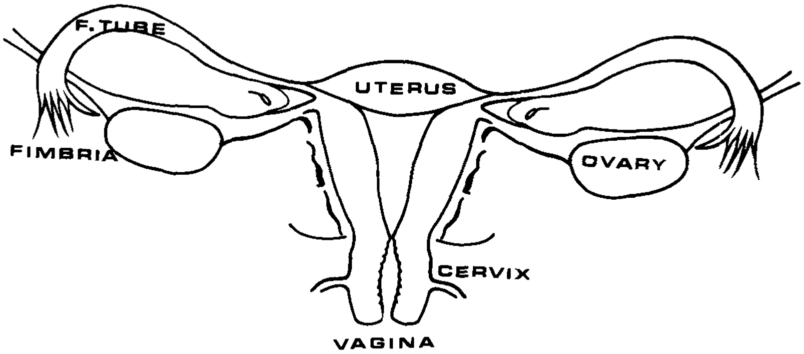


Fig. 1. Schematic representation of the female reproductive system pathways seen from in front.

particles originated from talc used to dust condoms.[12] In this circumstance, talc particles were probably thrusted by the penile pumping action during intercourse. Furthermore, Henderson et al. found talc particles deeply embedded in 75% of ovarian tumors studied.[13,14]

The potential harmful effects of talc on a highly differentiated tissue such as the ovary, with its interrelated cell types and cyclical changes of secretory activity, should certainly not be ignored.[15]

To demonstrate the upward migration of nonmotile, inert chemical substances we made use of radionuclide imaging and counting techniques.[16] During the course of the study, we came to recognize that the value of the images obtained outlining the female reproductive system pathways functionally reflected the dynamic state of this system and could be used as an additional and/or alternative diagnostic modality in clinical gynecologic practice in evaluating tubal patency. Diagnostic procedures where gases, fluids, dyes, and contrast medium are introduced through manual interventions under positive pressure from the uterine cervix into the peritoneum, are anatomically accurate and safe in the hands of those performing them regularly, but do not physiologically portray

Table 1. Possible Chemical Carcinogens Used in the Vagina for Cosmetic, Hygienic, and Medicinal Purposes*

1	Arsenicals
2	Hydroxiquinolines
3	Nitrofurantion
4	Ichthammol
5	Sulphonamides
6	Metronidazole
7	Nitrosamine†
8	Spermicides
9	Asbestos‡
10	Talc
11	Gentian violet

*From Venter.[5]
†Possible formation by chemical reduction.
‡As a contaminant.

Table 2. Incidence of Carcinoma of the Ovaries in Different Countries (per 100,000)*

Sweden	21.0
Norway	16.5
USA (whites)	15.6
England	14.7
Israel	11.0
USA (blacks)	8.8
USA (hispanics)	5.9
Africa	4.6
India	3.2
Japan	3.1

*From Kolstad and Beecham.[6]

Table 3. Surgical Indication and Operative Procedure (Group I)—24 Patients

No. Patients	Surgical Indication	Operative Procedure
4	Sterilization	Fimbriectomy
7	Ca. breast stage III	Bilateral salpingo-oophorectomy
1	Ca. breast stage III	Hysterectomy and bilateral salpingo-oophorectomy
2	Postmenopausal bleeding	Dilatation and curettage
2	Postmenopausal bleeding	Hysterectomy and bilateral salpingo-oophorectomy
3	Menorrhagia	Dilatation and curettage
4	Menorrhagia	Hysterectomy and bilateral salpingo-oophorectomy
1	Pelvic infection	Hysterectomy and bilateral salpingo-oophorectomy

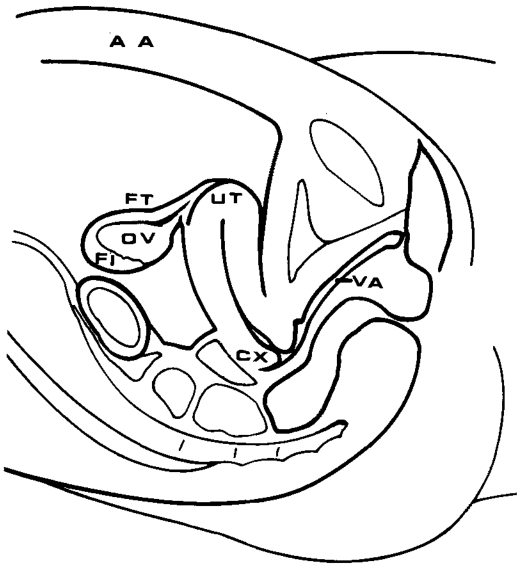


Fig. 2. Median sagittal section of female genitalia to show relationships in the position in which the study was carried out. AA, anterior abdominal wall; VA, vagina; CX, cervix; UT, uterus; FT, fallopian tube; FI, fimbria; OV, ovary.

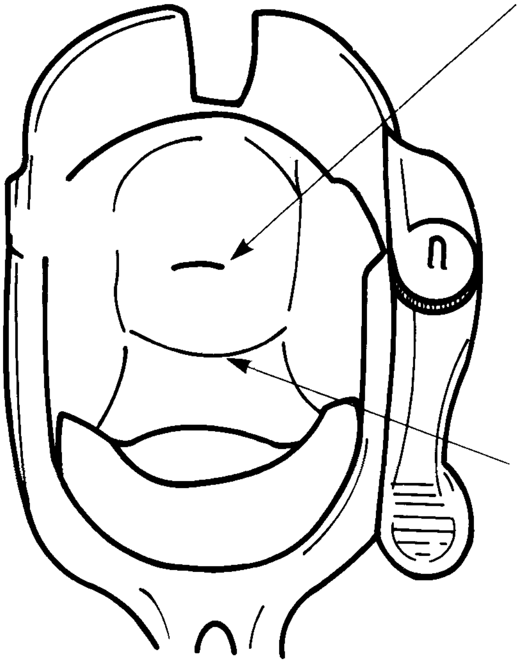


Fig. 4. Exposed cervix seen from in front with arrows showing external cervical os and posterior fornix where ^{99m}Tc-HAM is usually deposited during HERS.

fallopian tube patency. They are invasive procedures, uncomfortable for the patient, restricted under certain conditions, and not free of risks of hypersensitivity reactions inherent in any contrast medium.

MATERIALS AND METHODS

Patients in this study were divided into two different groups. Group I consisted of 24 adult women, both blacks and whites, admitted to hospital for elective gynecologic operations (Table 3). Group II consisted of 29 young white adult women referred by the Infertility Clinic for evaluation of their tubal patency. The radionuclide procedure was explained and the necessary consent was obtained.

Procedure

The patient was placed in the supine gynecologic examination position with the buttocks slightly elevated or in the Tredelenburg position. (Fig. 2). The cervix and posterior fornix were exposed with a Cusco vaginal speculum (Fig. 3) and 10 mCi (for patients of group I) and 2–3 mCi (for

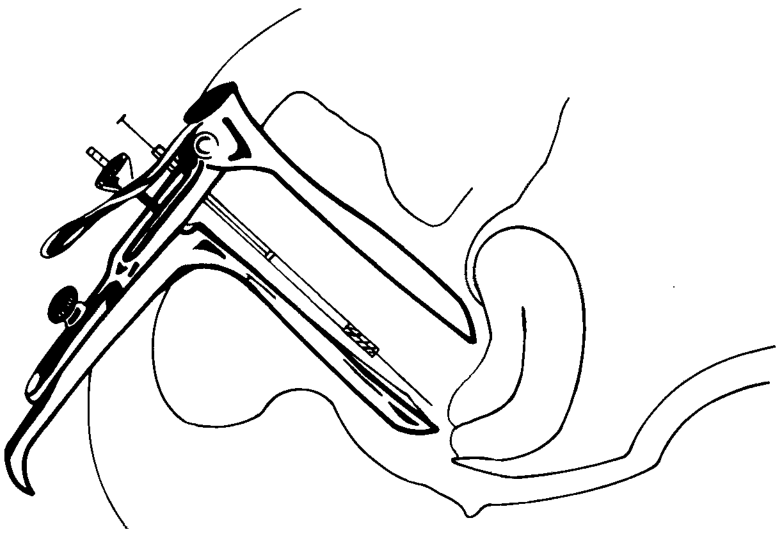


Fig. 3. Cervix exposed with a Cusco vaginal speculum and syringe in place for deposition of ^{99m}Tc-HAM for HERS.

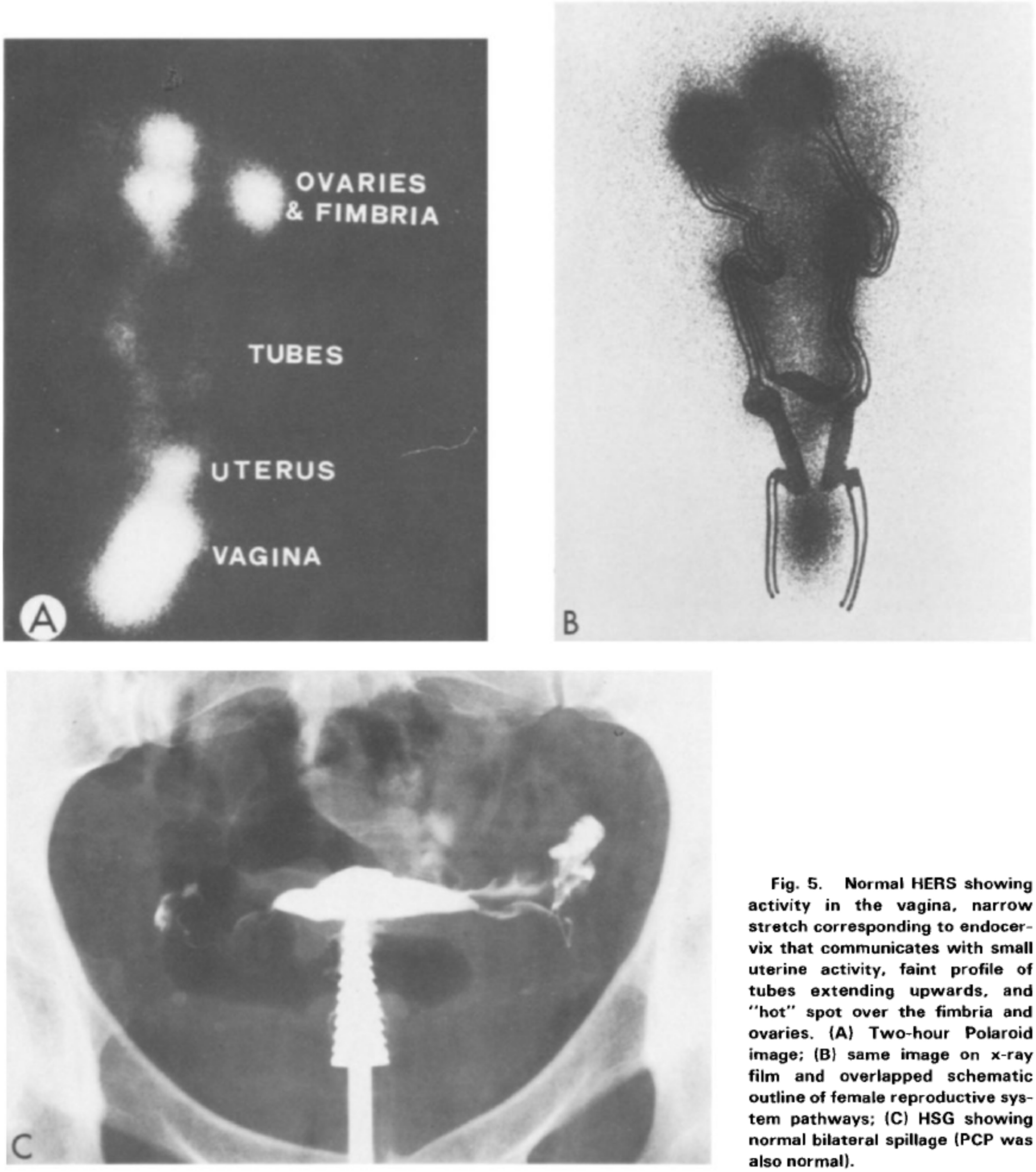


Fig. 5. Normal HERS showing activity in the vagina, narrow stretch corresponding to endocervix that communicates with small uterine activity, faint profile of tubes extending upwards, and "hot" spot over the fimbria and ovaries. (A) Two-hour Polaroid image; (B) same image on x-ray film and overlapped schematic outline of female reproductive system pathways; (C) HSG showing normal bilateral spillage (PCP was also normal).

patients of group II) of ^{99m}Tc-HAM in a volume of less than 1 ml were deposited in the posterior fornix, or close to the cervical external os (Fig. 4). The plastic cover of the needle (37 mm) was kept in place so as not to accidentally hurt the exposed tissue. The radionuclide was quickly discharged and the vaginal speculum carefully withdrawn while trying not to let the radioactive fluid leak out from the vagina. The vulva was then covered with a sanitary towel and the legs pressed or crossed together. The patient was kept in this position for the next 3 hr.

In patients from group I, about 24 hr after deposition of the radioactive tracer in the vagina, counts were performed on removed surgical specimens using a 12.7 cm well-scintillation detector. Where the uterus and adnexae were removed together, they were first counted as a whole and later separately. In the five patients that had D & Cs, only the endometrial scrapping was counted. In the case of fallopian tubes, each one was counted separately and the fimbria and ovaries separately from the isthmus. In two cases, a piece of the anterior peritoneum, fluid from the pouch of Douglas, peripheral blood, and lymphatic glands were also counted to determine the possibility of reabsorption of the radionuclide

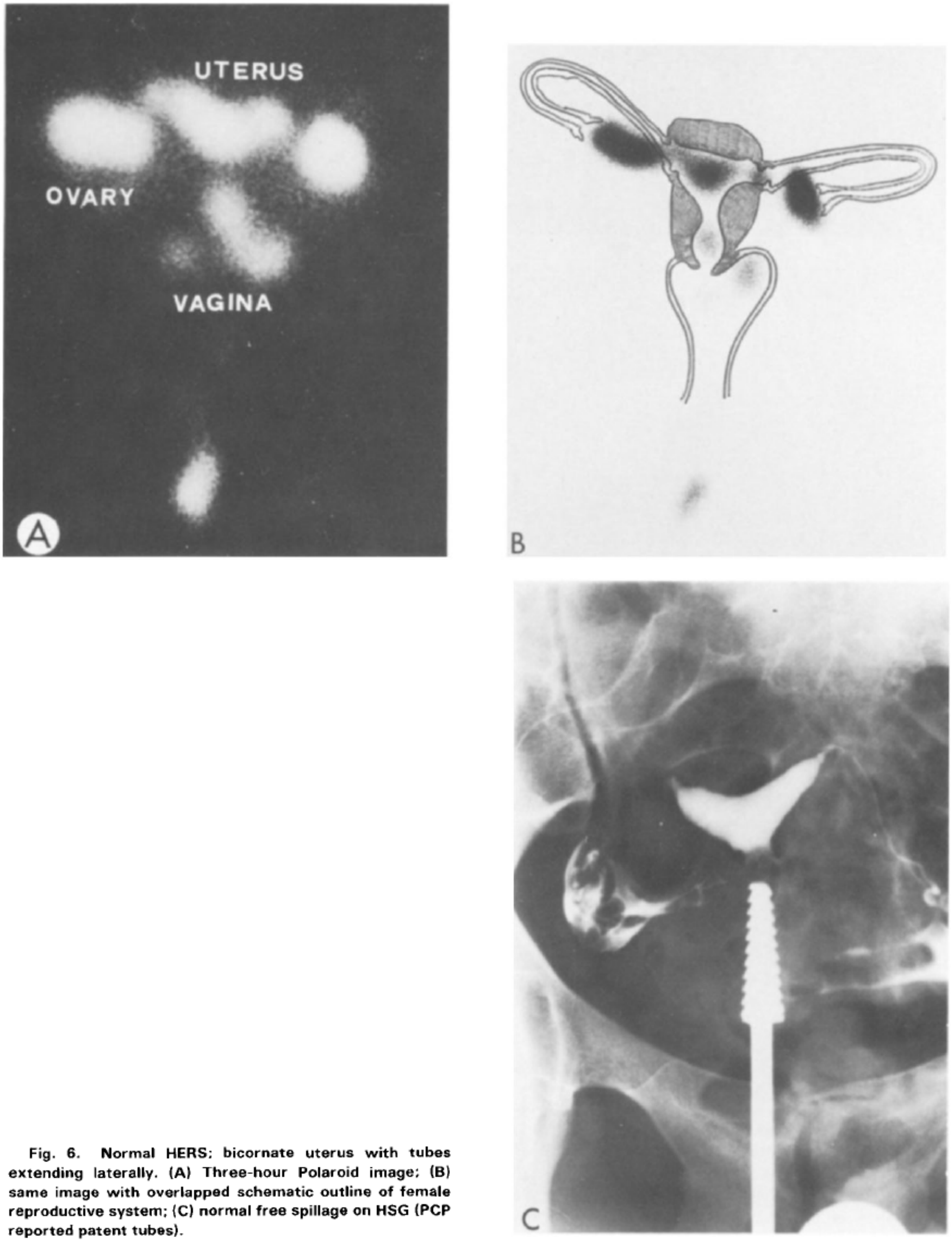


Fig. 6. Normal HERS: bicornate uterus with tubes extending laterally. (A) Three-hour Polaroid image; (B) same image with overlapped schematic outline of female reproductive system; (C) normal free spillage on HSG (PCP reported patent tubes).

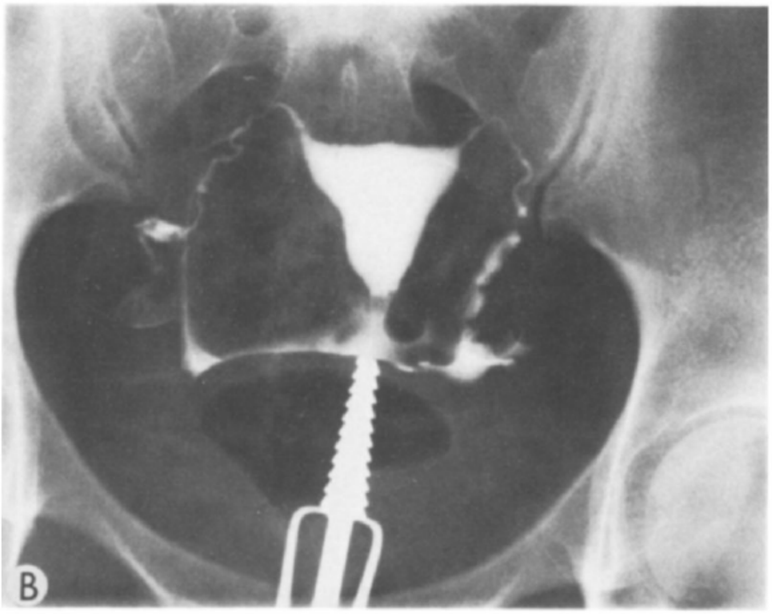


Fig. 7. (A) Normal HERS 1, 2, and 24 hr after deposition of ^{99m}Tc-HAM in posterior fornix of the vagina. (B) Patent tubes reported on HSG and PCP.

into the blood stream or lymphatic drainage from the vaginal mucosa.

If radioactivity levels measured on the removed surgical specimens were substantially higher than background levels, this constituted positive evidence of migration of the ^{99m}Tc-HAM from the vagina to the uterus or the tubes and ovaries. However, if radioactivity levels measured were comparable to background levels, it was taken as evidence that no migration of ^{99m}Tc-HAM had taken place and the cause for this possible obstruction was investigated.

Images were obtained 1, 2, 3, and 24 hr after deposition of the radioactive tracer on a large field of view gamma camera with a low-energy parallel all-purpose collimator, to a total of 400–500 K counts. The usual was an anterior view over the lower pelvic region, and in selected cases, images were also obtained shielding the high activity in the vagina in order to enhance the image of the uterus and tubes. Scintiphotos were recorded on Polaroid and x-ray film.

The normal pattern of the images obtained with this procedure would be a central elongated area of high activity over the vagina. Directly on top of this area would be a narrow stretch of activity corresponding to the endocervix, which would communicate the vagina and intrauterine activity. The uterus appeared as a smaller area of varying size, position, and shape (in most cases it was triangular). The tubes would be seen extending laterally or upward in a diverging angle with a distal "hot" spot of high intensity corresponding to the fimbria and ovaries (Fig. 5). In some cases, activity in the region of the tubal isthmus could not be visualized, although there was high activity in their distal segment (Figs. 6 and 7). In most cases, activity progressed within the first hour simultaneously through both tubes, while in others, activity moved faster in one tube than in the other, showing increased activity on one side. (Fig. 8). Scans were interpreted as abnormal if there was no activity in one or both tubes and specially if the distal focal area of high activity in the fimbria did not show up (Figs. 9, 10, and 11). Anatomic variants were also detectable (Fig. 12).

All patients of group II also had contrast hysterosalpingography (HSG) and peritoneoscopy (PCP) done after HERS. Spillage of the contrast media into the peritoneal cavity during HSG or appearance of the dye in the fimbria during PCP was an evident sign of tubal patency. The pressure exerted to introduce these substances from the

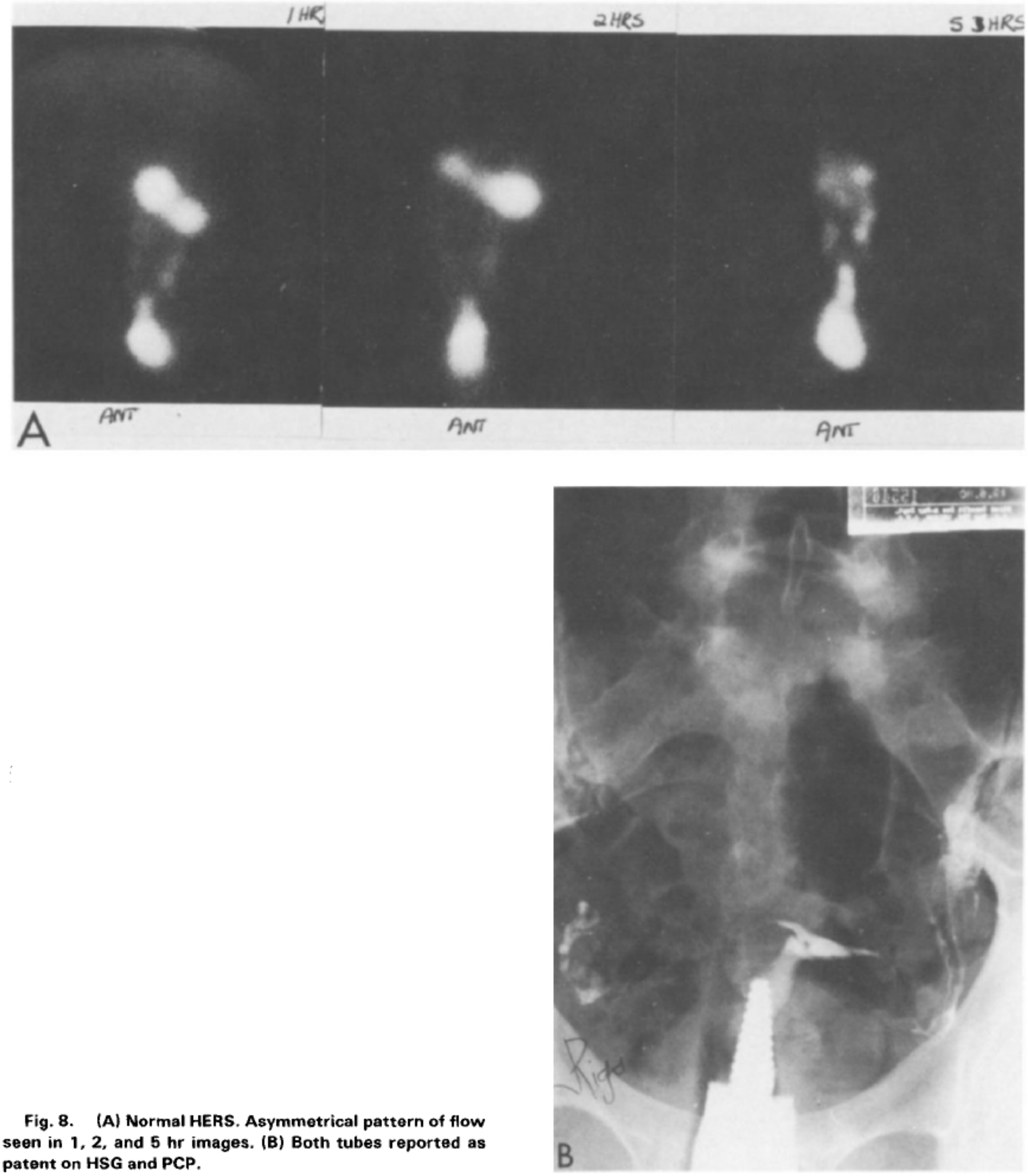


Fig. 8. (A) Normal HERS. Asymmetrical pattern of flow seen in 1, 2, and 5 hr images. (B) Both tubes reported as patent on HSG and PCP.

uterine cervix to the peritoneal cavity was also taken into consideration. Results of the three diagnostic procedures were later compared and clinically evaluated. (See Results below.)

Radiation exposure to patients of group I was low or in most cases negligible, since the target organs had been surgically removed. However, this was not the case for patients of group II who were sexually active and in potentially childbearing age.

We were concerned because the radioactivity reaching the fimbria and ovaries, which in this case were the target organs, decayed there physically, as there is no know mechanism for the biologic removal of the ^{99m}Tc-HAM once they reach the critically radiosensitive gonads. For this reason, we reduced the dose of the deposited ^{99m}Tc-HAM in the vagina to 2–3 mCi during the course of the study of patients from group II without sacrificing clinically informative value to the procedure.

Fortunately, most of the deposited radioactivity appears to be in the vagina and only a fraction of it migrates to the

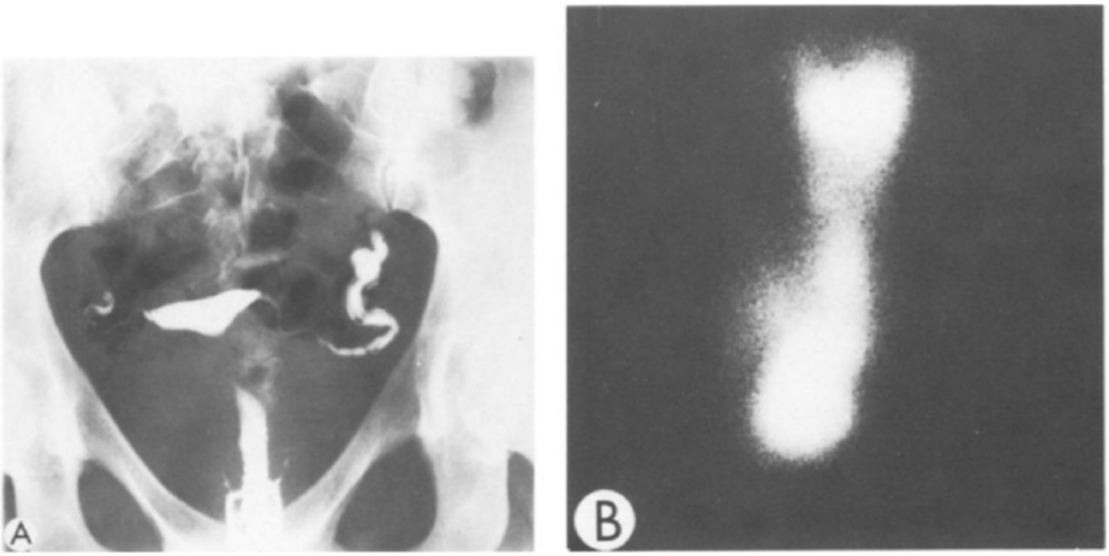


Fig. 9. **Patient with left side hydrosalpinx. (A) HSG shows a dilated and contorted left tube with a short and thin right tube. There was spillage in the left side with obstruction in the right side tube. (B) A 2-hr image of HERS shows the same pattern with no migration of ^{99m}Tc-HAM in the right tube.**

uterus and tubes (Fig. 13). Furthermore, in most cases this migration occurs within the first 3 hr and no further imaging is needed at 24 hr, which makes it possible to still obtain good quality images while reducing the radiation dose to the patient to safer levels comparable to those of x-ray diagnostic procedures.[17]

RESULTS

Because the radioactive material leaked out from the vagina in 3 patients, these patients were excluded from the final analysis of the 24 patients of group I (Table 4). In 16 of the

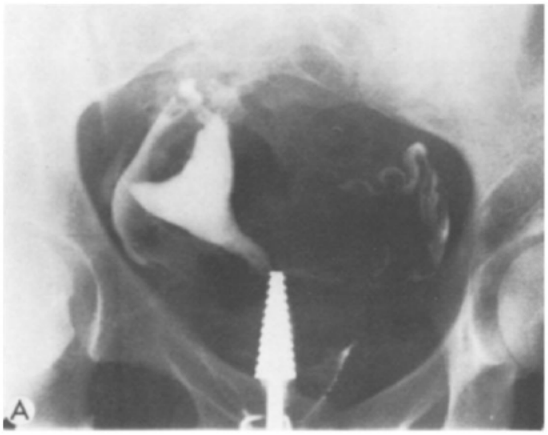
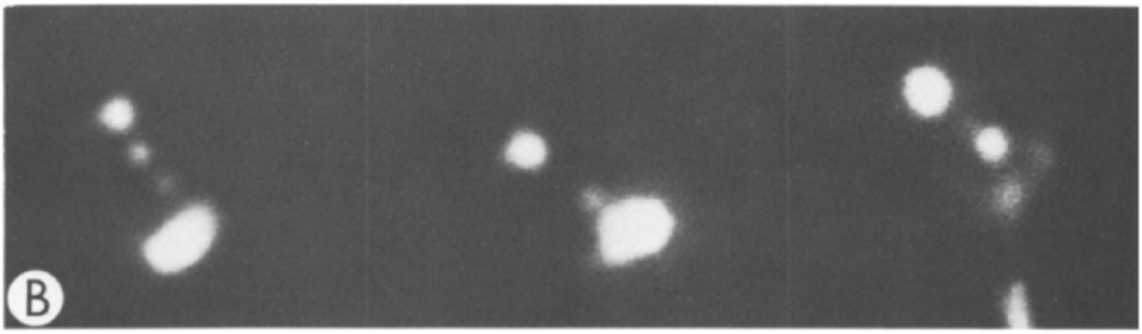


Fig. 10. **HERS and HSG (A) show uterus displaced to the right with long contorted left tube and obstructed right tube. (B) HERS on the 2, 3, and 24 hr images show focal "droplets" of higher activity at site of prominent kinks of left tube.**



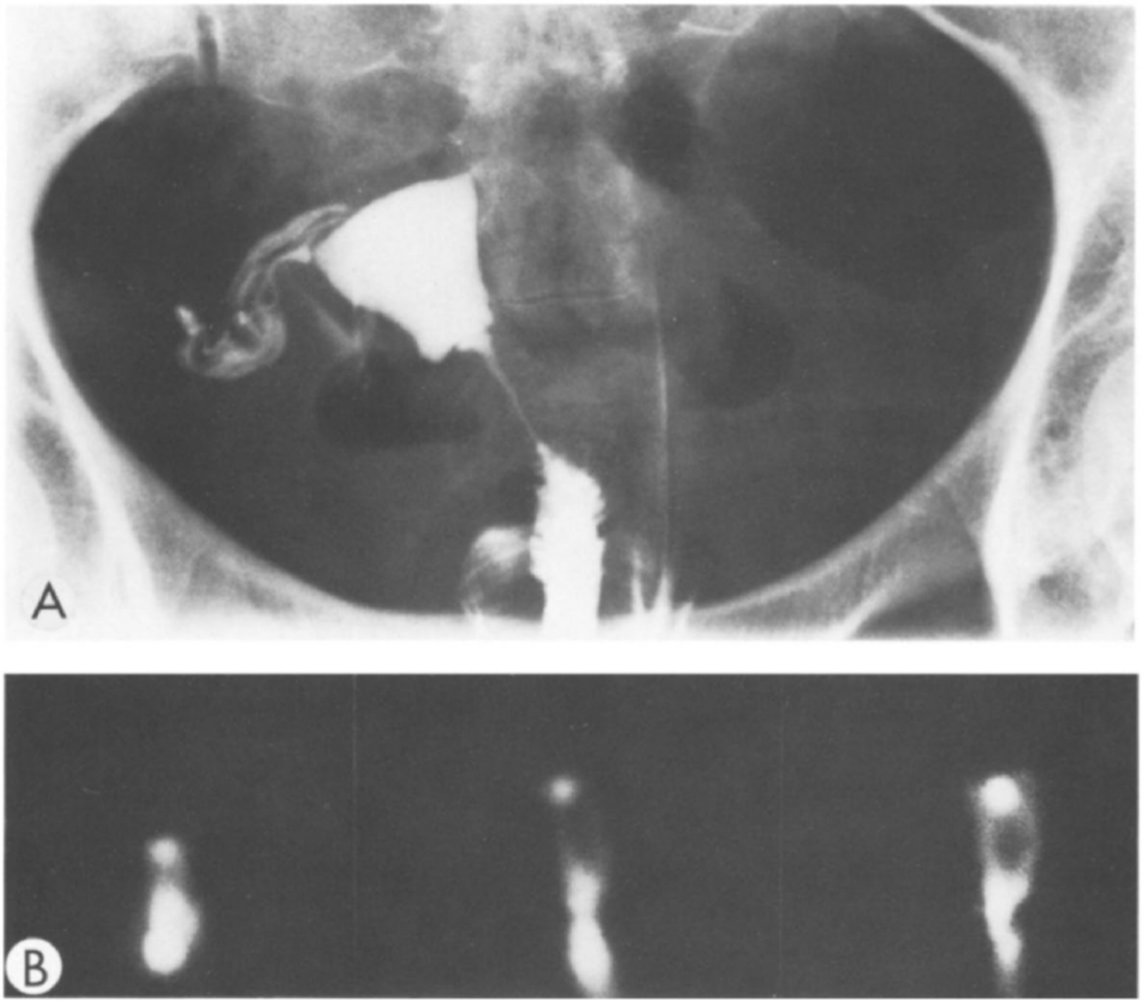


Fig. 11. (A) HSG shows right tube to be patent while the left tube is only seen in its proximal segment. (B) HERS shows the same pattern at 1 and 2 hr. Later, at 24 hr, activity can be seen migrating through left tube but not reaching the fimbria.

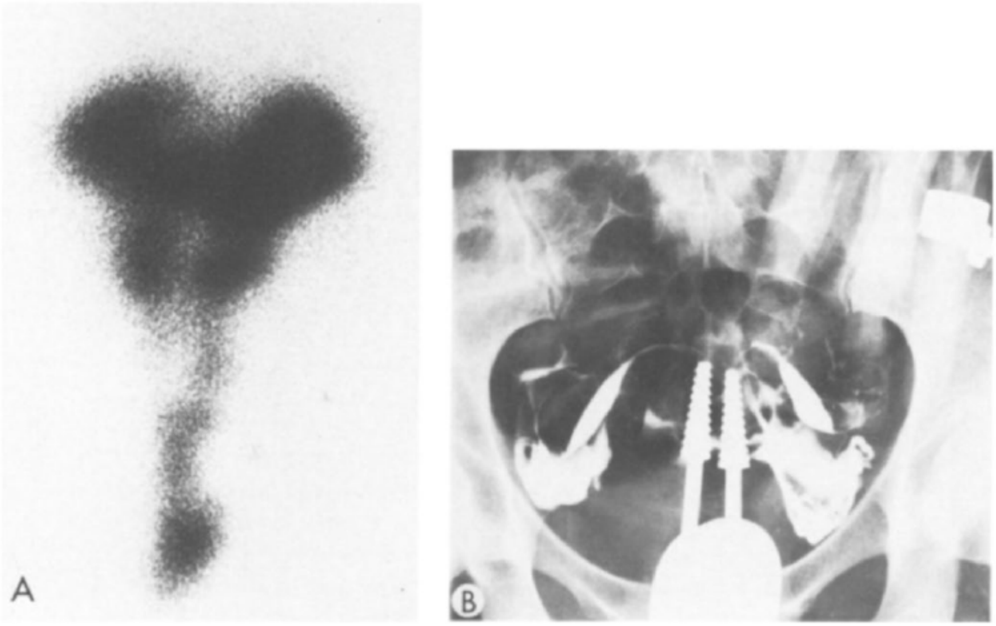


Fig. 12. Patient with didelphos as outlined on 1-hr image of HERS (A) and HSG (B).

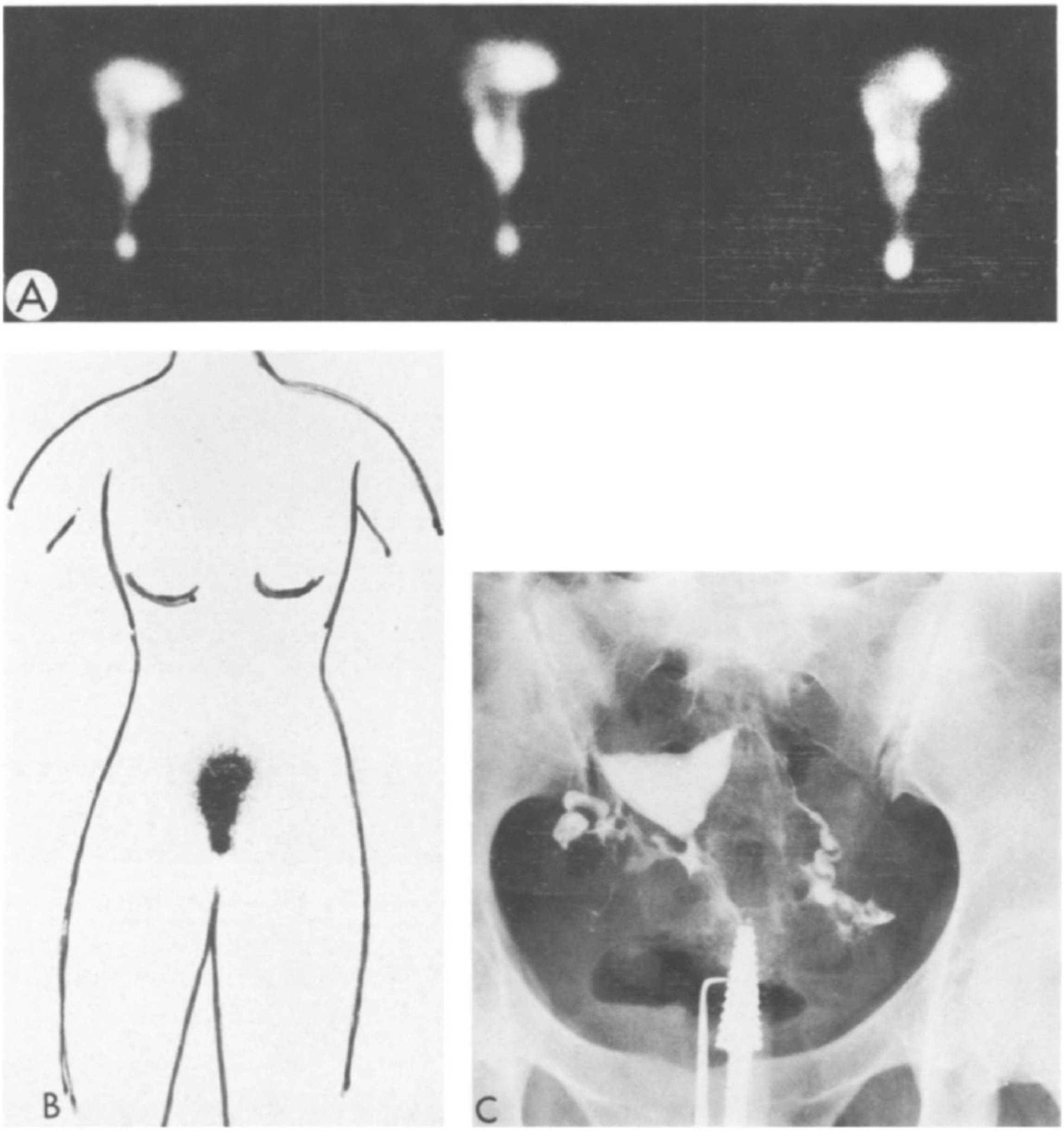


Fig. 13. (A) HERS shows a normal pattern of migration on 2, 3, and 24-hr images. (B) Twenty-four-hour whole body scan shows activity exclusively in the area of interest. (C) Bilateral tubal patency reported on HSG and PCP.

Table 4. Summary of Results (Group I)

Positive migration	16
Negative migration	
No passage to uterus	2
No passage to adnexae	3
Technically defective	3
Total patients examined	24

Table 5. HERS Versus HSG and PCP (Group II)

Agreement between HERS, HSG, and PCP	21
Disagreement between HERS/HSG and PCP	
HERS (−); HSG and PCP (+)*	5
HERS (+); HSG and PCP (−)	1
Technically defective	2
Total patients examined	29

*Tubes patent (+); tubes not patent (−).

remaining 21 patients there was positive evidence of migration of the ^{99m}Tc-HAM from the vagina to the uterus or the tubes and ovaries. The results were negative in 5 cases; in 2 of them the radioactive ^{99m}Tc did not pass from the vagina to the uterus, and in the other 3 there was no migration to the adnexae or fimbria.

In 14 of 21 cases, it was possible to measure high radioactivity levels in the adnexae separately from the uterus. Nine of these showed marked radioactivity in the tubes and ovaries (most of it localized in the fimbria). In 5 cases, radioactivity levels in the tubes were not much higher than the background, and in these patients severe tubal occlusion due to previous infection was confirmed by pathologic study of the surgically removed specimens. In the two patients where pieces of the anterior peritoneum, peripheral blood, and lymphatic glands were counted, the radioactivity levels of the samples were as low as that of the background. This showed that the ^{99m}Tc-HAM had not reached the adnexae through the blood supply owing to local reabsorption or lymphatic drainage from the vaginal mucosa where they had been deposited.

When HERS was compared with the results of HSG and PCP in group II (Table 5), we found that in 21 patients there was complete accordance between the 3 diagnostic modalities, be it that the tubes were patent or occluded. In one case, HSG and PCP showed that the tubes were patent, while initially HERS showed no migration in one tube during the first 3 hr of observation, but this changed later at 24 hr, when radioactivity appeared in the distal end of that tube (Fig. 14). In 6 cases there was no agreement between HERS and HSG and PCP. In 5 of them, both HSG and PCP showed that the tubes were patent when the contrast media and the dye were introduced under extreme pressure (Figs.

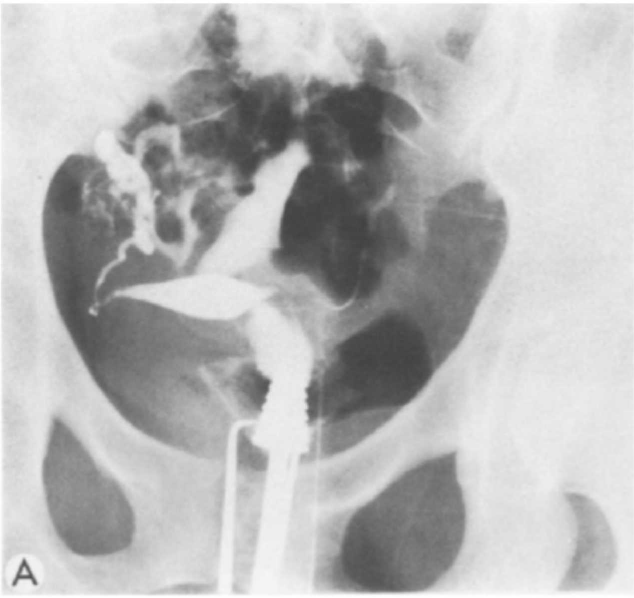
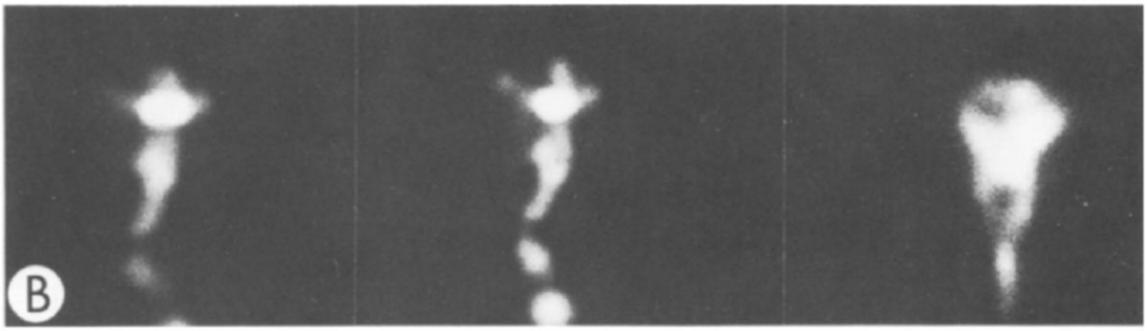


Fig. 14. (A) HSG shows bilateral tubal patency. (B) Two hour and 3 hr images on HERS show migration on left tube only, which appears to be long and contorted. At 24 hr, radioactivity appears to have migrated through right tube as well.



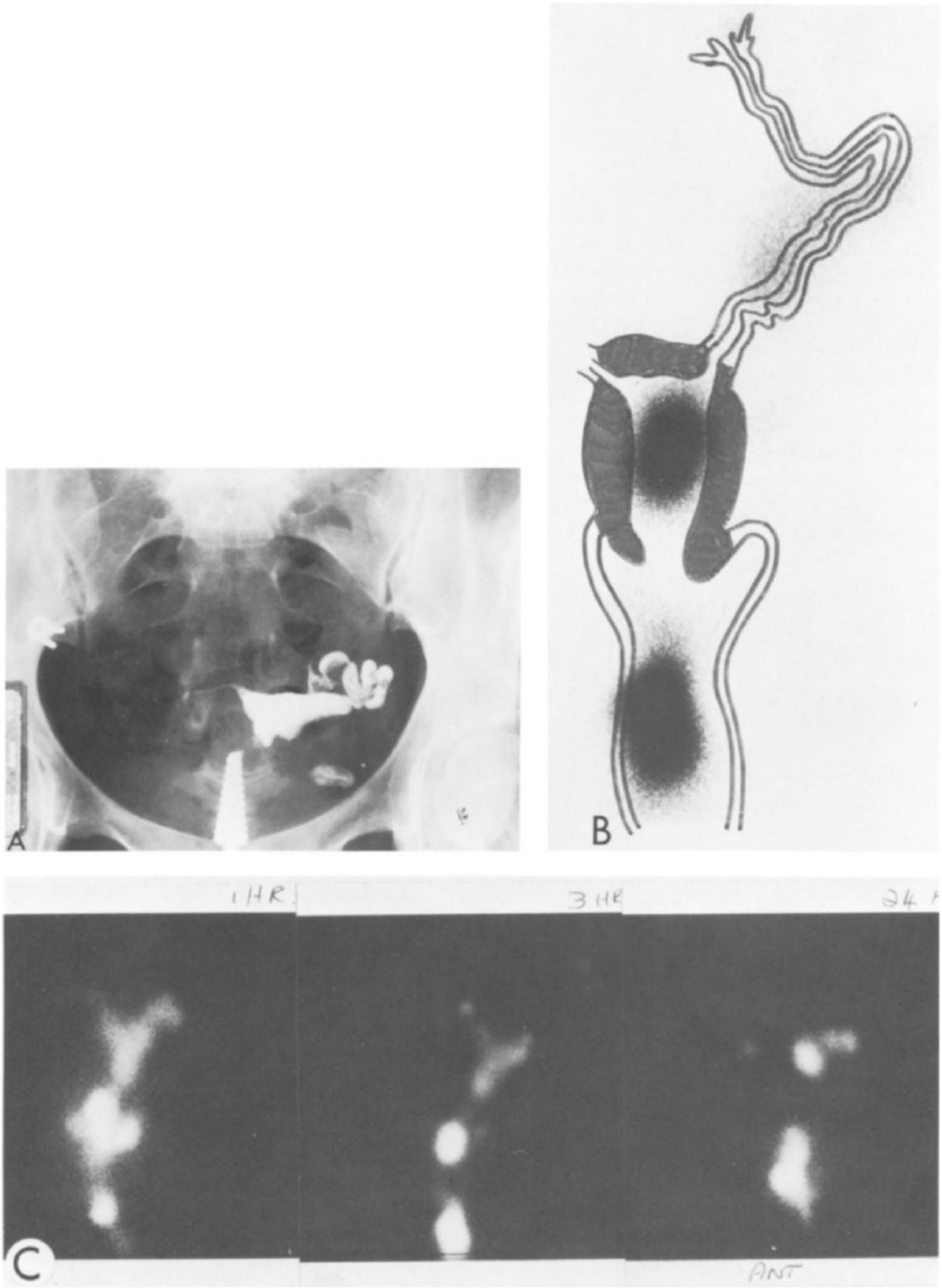


Fig. 15. (A) During HSG and PCP both tubes were reported to be patent, but only after introducing contrast media and dye, respectively, under extreme pressure. (B and C) HERS shows that up to 24 hr, there is no migration through the right tube, while the left tube appears long and kinked.

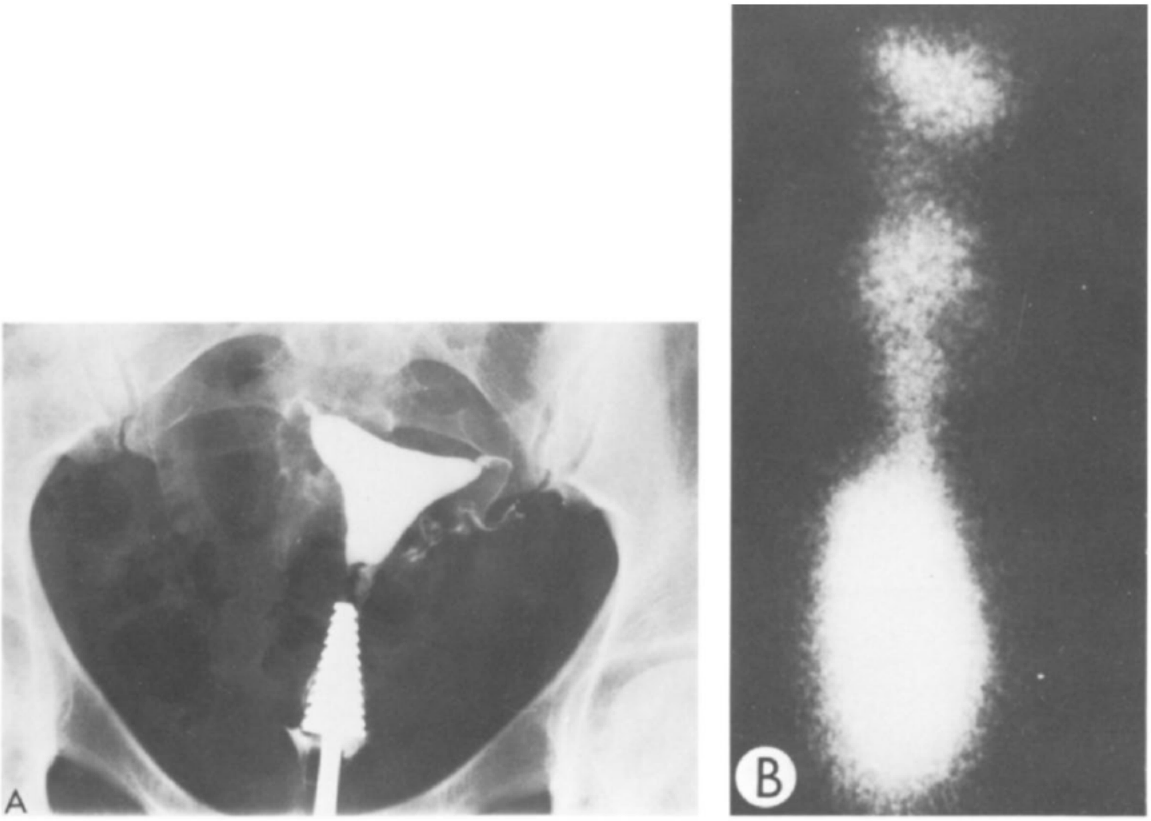


Fig. 16. (A) During HSG and PCP, both tubes were reported to be patent, but only after introducing contrast media and dye, respectively, under extreme pressure. (B) On the 24-hr image, HERS shows no migration of ^{99m}Tc-HAM through the right tube.

15 and 16). In these 5 cases, HERS showed no evidence of migration in one or the other tube, reflecting in this way the physiologic state of the fallopian tubes. In only one case did HERS show patency in one tube, while HSG and PCP did not, this was in the case of a woman with a septum in her vagina and a double uterus where manipulations for HSG and PCP were difficult. Finally, in 2 cases the results were equivocal because at least 2 of the 3 diagnostic procedures were technically deficient and no clinical information of diagnostic value could be obtained.

DISCUSSION

The results obtained from HERS in patients from group I clearly demonstrate the upward migration of a particulate radioactive tracer such as ^{99m}Tc-HAM from the vagina through the uterus and tubes into the peritoneal cavity and ovaries. This evidence correlates with findings on the surgically removed specimens, proving the accuracy of this radionuclide procedure. The real importance of this finding is that it supports previous evidence for the migration of inert, nonmotile chemical substances from the vagina to the peritoneum and ovaries,[11–14] and could help explain the role that some of these apparently innocent and frequently used substances play in the etiology of certain gynecologic diseases.[3,4,8,9]

The mechanism by which this migration takes place is not clearly defined, but it is assumed that it is a combination of muscular peristaltic movements, changes in peritoneal pressure, and ciliary motion (in the tubes) that drives particles from the vagina to the peritoneum and ovaries. The abundance of blood vessels interspersed with muscle bundles and active mucosal secretion form in the fimbria a kind of erectile tissue where most of the tubal activity tends to gravitate. There must also be a cyclical hormonal component regulating this process, and we

presume that migration is facilitated during the period of ovulation.

As far as the radionuclide imaging process is concerned, it was encouraging to find a close correlation of this procedure when compared with HSG and PCP. But most important of all is the fact that HERS functionally reflects the dynamic state of the female reproductive system pathways by showing particulate migration, which is not the case of the other anatomically dependant diagnostic modalities used to evaluate tubal patency. In this small series we found that in five cases, HSG and PCP were reported showing anatomical tubal patency only because both the contrast media and dye were injected under extreme pressures, opening tubes that under other circumstances would not be patent. HERS proved in these five patients (19% of the series) that there was no migration of ^{99m}Tc-HAM through the fallopian tubes, this being the probable cause for the infertility of these patients.

Even though HERS is a simple, safe, and accurate procedure, further studies will be necessary to establish its value as an additional and/or alternative study to other conventional procedures in evaluating tubal patency and its role as a functional radionuclide imaging modality in clinical gynecologic practice.

One indication for HERS would be to use it as a procedure to monitor the efficacy of sterilization procedures where the fallopian tubes are dissected or obstructed; or conversely to see if they are patent and open to transit after reconstructive surgery in patients that have been previously sterilized. In both cases the patient becomes her own control before and after the surgical procedure.

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Exhibit 28

The Transport of Carbon Particles in the Human Female Reproductive Tract

G. E. Egli, M.D., and Michael Newton, M.D.

THE METHOD by which spermatozoa reach the oviduct remains an important problem in mammalian reproduction. Since spermatozoa possess motility, it has been widely assumed to be the most important factor. However, work in cows suggests that it may not be the chief means of transport. Thus, Vandemark and Moeller recovered spermatozoa from the oviduct 2½ min. after mating. This is far sooner than could be expected on the basis of the inherent motility and sense of direction of spermatozoa.

Work in animals indicates that muscular contractions of the reproductive tract may aid in the transport of spermatozoa and that the oxytocic hormone may play a part in this process. Vandemark and Hays[11] noted that a crescendo of uterine contractions took place before and during copulation in the cow. Furthermore, stimulation of the cow's genitalia produced a rise in intramammary pressure.[7] Normally such a change is brought about by the release of oxytocin from the posterior pituitary gland during the letdown or ejection reflex as the calf or milking machine is applied to the teat.[5] Finally, in-vitro studies by Vandemark and Hays[12] demonstrated that when oxytocin was added to the solution perfusing the isolated cow's uterus, the rate of transport of spermatozoa was increased.

Evidence that the same process occurs in humans is scanty. Because of the difficulty of using spermatozoa, inert particles have occasionally been employed experimentally. Amersbach placed a cap containing a suspension of carbon particles over the cervix. Following coitus he was able to recover

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particles from the cervical canal. Trapl had a patient insert carmine particles into the vagina immediately after intercourse. Twenty-four hr. later at laparotomy he found numerous particles in the uterine tubes. Furthermore, it has been suggested that there may be a sucking effect as a result of uterine contractions occurring at orgasm that pulls semen through the cervix into the uterus.[8] There is also some evidence that oxytocin is released at the time of orgasm in humans.[4, 9] However, the time relationships and precise mechanisms of transport of inert particles or spermatozoa have not been elucidated in humans. The paucity of information in this regard has been pointed out by Hartman in his excellent review article.

If human spermatozoa move at a rate of 3 mm./min.,[3] it should take a spermatozoon, moving on a direct course, at least 45 min., in the average woman, to travel from the cervix to the junction of the middle and outer thirds of the tube, where fertilization occurs. If the action of the uterine or other muscles of the reproductive tract is important in humans, then not only spermatozoa but also inert particles should reach the tube much sooner than this. The present study was designed to determine whether, under reasonably controlled conditions, carbon particles could be transported quickly from the vagina to the tubes.

METHODS

It seemed desirable to set up, as far as possible, conditions that were optimal for rapid transport. Thus, patients were selected who required an elective abdominal hysterectomy that could be scheduled at or near the day of ovulation. They had to be of reproductive age, to have proved fertility, and to have relatively normal reproductive organs. A suspension of carbon particles in Dextran was made up so that the particles were similar in size to spermatozoa and that the solution was of the consistency of seminal fluid. This was done by mixing 30% Dextran with 4% bone black. In addition, it was decided to use intramuscular oxytocin to aid in the transport of the particles, because of the experimental evidence indicating its possible importance.

Three women fulfilling the above criteria were studied. In each instance the procedure was as follows: Soon after general anesthesia had been induced, the patient was placed in the lithotomy position with her head tilted downward at an angle of 15° from the horizontal. A speculum was introduced into the vagina, and 3–4 ml. of sterile carbon particles–Dextran suspension were deposited in the posterior fornix. At the same time 1 ml.

(10 U.) of oxytocin was given intramuscularly. The speculum was removed, and the patient was immediately returned to the supine flat position. Her abdomen was promptly opened, and before the uterus was manipulated, a suture was placed tightly around the tubes about 1 cm. lateral to the uterus. The tubes were excised and taken to the laboratory, where they were flushed with saline from the infundibular portion downward. The solution was collected on clean slides and examined under the microscope for carbon particles.

RESULTS

The first patient was 32 yr. of age, gravida 6, para 6, and was at the fourteenth day of her cycle, which was usually about 28 days in length. Twenty-eight min. after the carbon-particle suspension had been deposited in the posterior fornix, the tubes were ligated and then excised. Many carbon particles were found in the washings from both tubes. On microscopic examination the endometrium was described as being early progestational.

The second patient was 30 yr. of age, gravida 6, para 6, and was at the twelfth day of her cycle, which was usually about 28 days in length. Thirty-four min. after the carbon-particle suspension had been deposited in the posterior fornix, the tubes were ligated and then excised. Carbon particles were recovered from both tubes. On microscopic examination the endometrium was described as being estrogenic.

The third patient was 41 yr. of age, gravida 8, para 7, aborta 1, and was at the thirteenth day of her cycle, which was usually about 28 days in length. She was a diabetic and had aborted three mo. previously. Twenty min. after the carbon-particle suspension had been deposited in the posterior fornix, the tubes were ligated and then excised. No carbon particles were found in the washings from either tube. On microscopic examination the endometrium was described as being early progestational.

DISCUSSION

This study indicates that in two cases, under the conditions outlined, inert carbon particles, placed in the posterior fornix of the vagina, were found 28 and 34 min. later in both tubes. How they reached the tubes is a difficult question to answer. Certainly they did not proceed by their own movements. It is reasonable to suppose that some sort of movement of the uterus and/or tubes contributed to the transport of the particles.

Movements of the reproductive organs and particularly the uterus could be due to inherent motility, general body movements, the effect of anes-

thesia, or the influence of the injected oxytocin. The uterus undoubtedly possesses inherent motility. Conceivably this could be sufficient to aid the transport of particles into the tubes, although it might well have been decreased by the anesthesia used. Bodily movements were held to a minimum. The patients were on their backs at all times, and so virtually no opportunity for the suspension to enter the uterus or tubes by gravity was afforded. Manipulation consisted only of removing the speculum, returning the patient to the supine position, opening the abdomen, and ligating the tubes. The effect of anesthesia would be, in general, to reduce uterine motility: However, spasm of the cervix or uterotubal opening could have been relaxed by the anesthesia. The theory that oxytocin does contribute to the transport of particles is most attractive, but at the present time we have no proof of it. Further in-vivo and in-vitro experiments are being done in pursuit of a solution to this problem.

The fact that in one case transport of carbon particles to the tubes was not demonstrated is not surprising. One of several factors may have contributed to this. Possibly the hormonal conditions present in the uterus were not optimal.[2] The patient's recent abortion may have been important. Finally, it is conceivable that insufficient time was allowed for transport.

SUMMARY AND CONCLUSIONS

Carbon particles, suspended in 30% Dextran, were placed in the vagina in three anesthetized women who were about to undergo elective abdominal hysterectomy at about the time of ovulation. At the same time oxytocin was injected intramuscularly. In two of the three women carbon particles were recovered from the tubes 28 and 34 min. later.

These data, together with other work in animals and humans, support the belief that the motility of spermatozoa is not the chief factor in sperm transport. Contractions of the muscle of the uterus or other reproductive organs may be very important, and it is possible that oxytocin may play a part in this process.

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